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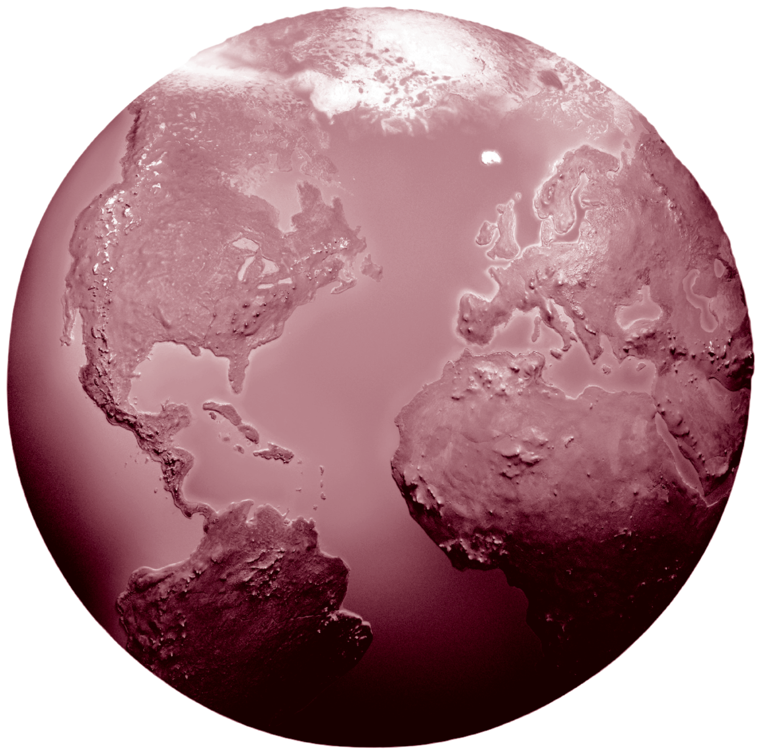

COMMENTARY BY THE HEI REVIEW COMMITTEE

Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN)

Andersen et al.

Health Effects Institute

Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN)

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with a Commentary by the HEI Review Committee

Research Report 214

Health Effects Institute

Boston, Massachusetts

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CONTENTS

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the Institute

- Identifies the highest-priority areas for health effects research
- Competitively funds and oversees research projects
- Provides intensive independent review of HEI-supported studies and related research
- Integrates HEI's research results with those of other institutions into broader evaluations
- Communicates the results of HEI's research and analyses to public and private decision-makers.

HEI typically receives balanced funding from the U.S. Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 380 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 260 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

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Research Report 214, *Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN)*, Z.J. Andersen et al.

INTRODUCTION

The coronavirus (COVID-19*) pandemic created unprecedented conditions that lent themselves to timely and novel air pollution research aimed at exploring key policy-relevant questions. As described in the Preface to this report, HEI issued Request for Applications 20-1B: Air Pollution, COVID-19, and Human Health. This RFA solicited applications for research on novel and important aspects of the intersection of exposure to air pollution and COVID-19 health outcomes. Specifically, HEI was interested in accountability studies that considered the effects of the unprecedented interventions taken to control the pandemic on emissions, air pollution, and human health, and in studies that considered whether populations who had been exposed to higher levels of air pollution were at greater risk of mortality from COVID-19 compared with others.

In response to the RFA, Dr. Zorana J. Andersen of the University of Copenhagen submitted an application to HEI titled "Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN)." Dr. Andersen proposed to use a population-based nationwide cohort of Danish adults to investigate whether long-term exposure to air pollution is associated with increased risk of COVID-19–related morbidity and mortality and to identify the most susceptible groups by age, sex, socioeconomic status (SES), ethnicity, and comorbidities. HEI's Research Committee recommended funding Dr. Andersen's proposed study because it thought it had several strong features, particularly the national population-wide cohort with individual-level data and fine-resolution exposure data. This Commentary provides the HEI Review Committee's independent evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

Dr. Zorana J. Andersen's 1-year study, "Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN)," began in March 2021. Total expenditures were $224,036. The draft Investigators' Report from Andersen and colleagues was received for review in November 2022. A revised report, received in April 2023, was accepted for publication in April 2023. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in both the Investigators' Report and the Review Committee's Commentary.

SCIENTIFIC BACKGROUND

Research from toxicology, human clinical studies, and epidemiology have linked air pollution exposure with risk of acute lower respiratory infections (i.e., bronchitis, bronchiolitis, and pneumonia), influenza, and respiratory syncytial virus (Monoson et al. 2023; Thurston et al. 2017). Research on such respiratory infections is complicated, however, and has had mixed results regarding the role of air pollution (HEI 2022; Loaiza-Ceballos et al. 2022).

Some early studies on air pollution and COVID-19 suggested potential associations (Bashir et al. 2020; Travaglio et al. 2021; Wu et al. 2020; Yao et al. 2020), but their ability to identify people who were infected or seriously ill with COVID-19 was so fraught with errors (which had very high potential to be correlated with air pollution) that the potential for biased results was very high. These early studies also missed important confounders, and results were difficult to compare and generalize due to different study designs, approaches to exposure estimation (i.e., short-term vs. long-term exposures), and outcome definitions (e.g., disease incidence, prevalence, severity, or case fatality rates). Moreover, nearly all of the first studies published on this topic were based on cross-sectional analyses or ecological study designs (including those mentioned above and Coker et al. 2020; Cole et al. 2020; Konstantinoudis et al. 2021; Liang et al. 2020) that compared area-based estimates of pollution (e.g., averaged across counties or postal codes areas) with area-based rates of disease incidence or mortality, for which individual-level risks cannot be derived.

Three early reviews (Copat et al. 2020; Katoto et al. 2021; Villeneuve and Goldberg 2020) all concluded that although the early body of evidence indicated that both short-term and long-term exposure to air pollution could affect COVID-19 outcomes, all studies to date had moderate to high overall risks of bias that precluded them from providing any insight into potential causal associations.

* A list of abbreviations and other terms appears at the end of this volume.

At the time that Dr. Andersen's study began, the available literature therefore included little high-quality evidence. Given the many design limitations of the previous studies on this topic, it was important to conduct the Andersen study, which aimed to overcome many of them.

SUMMARY OF APPROACH AND METHODS

STUDY OBJECTIVES

The overarching goals of Dr. Andersen's study were to investigate whether long-term exposure to air pollution is associated with increased risk of COVID-19–related mortality and morbidity and to identify the most susceptible subgroups of the population. Specifically, the investigators proposed the following aims:

1. Examine whether long-term exposures to fine particulate matter <2.5 µg/m^3 in diameter ($PM_{2.5}$), particulate matter <10 µg/m^3 in diameter (PM_{10}), black carbon (BC), nitrogen dioxide (NO_2), and ozone (O_3) are associated with risk of COVID-19 incidence, hospitalizations, or deaths in the general population.
2. Identify groups that are susceptible to air pollution–related COVID-19 outcomes by age, sex, SES, ethnicity, and comorbidity with several cardiometabolic and respiratory diseases and dementia.
3. Examine whether long-term exposures to $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3 are associated with poorer prognosis in people who tested positive for COVID-19, in terms of higher risk of hospitalization and mortality.

Briefly, the investigators 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 individual and community-level demographic and socioeconomic information. They assigned annual estimates of $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3 based on the year 2019 to each participant's residential address using chemical transport models. 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.

The investigators conducted many additional analyses, including testing for effect modification of any associations according to age, sex, SES, 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 used similar statistical approaches to those in the main analyses to examine associations between pollutants and COVID-19 hospitalization and death in a subgroup of individuals who had tested positive for COVID-19. The datasets and statistical approaches used in these analyses are described in greater detail in the following sections.

METHODS AND STUDY DESIGN

Study Population

Andersen and colleagues created a national cohort of all Danish residents who were 30 years of age or older on March 1, 2020, and who had lived in Denmark for at least 1 year prior to that date. They compiled individual information for participants for the year 2019 from the Danish national registers, including information on marital status, education, occupational status, wealth, family or household income, ethnicity, and household size. They also included several contextual variables that described the communities in which people lived. These contextual variables were defined at the parish level with data from 2019 and included population density, mean income, median wealth, percent unemployment, percent primary or lower education, SES difference between municipality and parish, municipality-level access to healthcare, lung cancer incidence rate, and diabetes incidence rate.

The investigators also linked data from the Danish National Patient Register to identify whether participants also had relevant comorbidities, namely cardiovascular disease, respiratory disease, lung cancer, diabetes, or dementia. Finally, they linked cohort participants to COVID-19 data from the Danish Health Authority to define the following COVID-19–related outcomes: incidence (defined as first positive polymerase chain reaction [PCR] test), hospitalization (defined as hospital admission for more than 12 hours within 14 days after the first positive PCR test), and death (defined as death from any cause within 30 days of the detection of a COVID-19 infection). These definitions for COVID-19 incidence, hospitalization, and death are key study design details that will be discussed below.

Exposure Assignment

Andersen and colleagues used information from the integrated Danish Eulerian Hemispheric chemical transport model, which is an atmospheric chemical transport model developed to study the long-range transport of air pollution across the Northern Hemisphere (Brandt et al. 2012), and the Urban Background Model, which is used for calculating background air pollution over Denmark with high spatial resolution (Brandt et al. 2003) to derive exposure estimates. For their main analyses, they assigned annual estimates of $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3 from the models for the year 2019 at a 1 × 1 km spatial resolution to cohort participants' address of residence at baseline (i.e., March 1, 2020).

Additionally, they assigned annual mean concentrations of $PM_{2.5}$, BC, NO_2, and O_3 for the year 2010 at a 100 × 100 m spatial resolution from the European-wide hybrid land use regression (LUR) model (de Hoogh et al. 2016) developed within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (*http://www.elapseproject.eu/*). This model was developed with a combination of observations from ground-based monitors, satellite data, dispersion model estimates, land use data, and traffic variables.

Main Epidemiological Analyses

The main statistical analyses for this study consisted of Cox proportional hazard models to examine associations between air pollution exposure in single-pollutant models and COVID-19 outcomes, following cohort participants until the date of death, emigration, or the end of follow-up on April 26, 2021. The investigators explored models with three levels of increasing adjustment for potential confounders. Model 1 adjusted for calendar time, age, sex, and region of residence; Model 2 added the individual-level variables listed above (i.e., marital status, highest completed education, occupational status, individual wealth, family income, and household size); and Model 3 added the contextual-level variables (i.e., municipality-level access to healthcare and parish-level population density, mean income, median wealth, percent unemployment, percent primary or low education, and the SES difference between municipality and parish). Hazard ratios (HRs) were estimated per interquartile range increases in exposure estimates, namely 0.55 μg/m^3 for $PM_{2.5}$, 1.14 μg/m^3 for PM_{10}, 0.09 μg/m^3 for BC, 3.49 μg/m^3 for NO_2, and 2.79 μg/m^3 for O_3.

Additional Epidemiological Analyses

The investigators performed many sensitivity analyses. Because there were changes over time due to differences in testing capacity, various pandemic-related restrictions and protection measures, and COVID-19 strains, they estimated associations separately in two pandemic waves, namely March 1 to July 31, 2020, and August 1, 2020, to April 26, 2021. They also evaluated effect modification of the associations between exposures and the various outcomes by age, sex, SES, ethnicity, and comorbidities.

The investigators used similar statistical approaches to those in the main analyses to examine associations between exposure and COVID-19 hospitalization and death in a subgroup of individuals who had tested positive for COVID-19 (i.e., hospitalization or death within 30 days of a positive test). They also examined models in which they controlled for municipality-level monthly COVID-19 positivity rates and estimated exposure–response functions to evaluate the shape of the associations between pollutants and each outcome by applying natural cubic splines with three degrees of freedom. Finally, they examined two-pollutant models for pollutant combinations where the Pearson correlation coefficient was less than 0.7 and replicated their main analyses with the ELAPSE-derived pollutant exposures.

SUMMARY OF KEY FINDINGS

COHORT AND EXPOSURE CHARACTERISTICS

The full study cohort included 3,721,813 Danish adults. In total, 138,742 individuals tested positive for COVID-19, 11,270 were hospitalized, and 2,557 died from COVID-19 during the 14 months of follow-up. Subjects who died or who were hospitalized from COVID-19, or those who died from any cause, were more likely to be men, less highly educated, unemployed, not married or living with a partner, or having lower income, as compared to those in the full cohort. The vast majority of positive tests, hospitalizations, and deaths were observed in the second pandemic wave.

Mean estimates of annual exposures (and standard deviations) to $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3 in 2019 based on the main exposure model were 7.4 (0.5), 12.7 (0.9), 0.3 (0.1), 10.7 (2.4), and 54.5 (2.2) μg/m^3, respectively, and were slightly higher among COVID-19 cases than for the total population.

Exposures estimated by the ELAPSE model were higher than those estimated by the main model, but they showed moderate to good correlation with each other (e.g., $r = 0.51$ for $PM_{2.5}$, 0.63 for NO_2, and 0.47 for both BC and O_3).

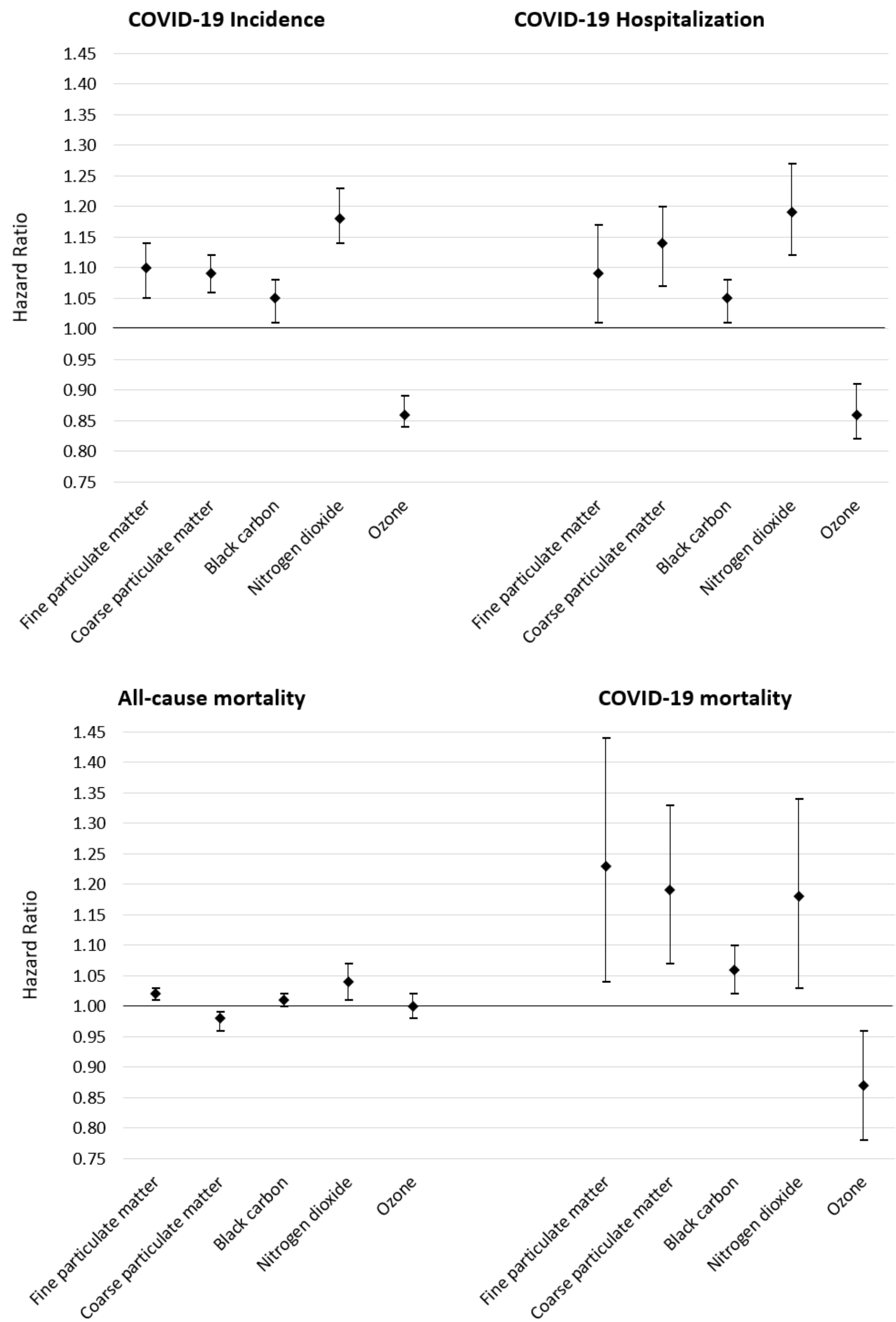
EPIDEMIOLOGICAL RESULTS

Main Findings

Andersen and colleagues found elevated risks of all three COVID-19 outcomes associated with exposures to $PM_{2.5}$, PM_{10}, BC, and NO_2 (**Commentary Figure**). They found inverse associations, however, between exposure to O_3 and the three outcomes. Estimates of risk for the COVID-19 outcomes were largely unchanged after adjustment for the individual-level characteristics (i.e., Model 2 compared to Model 1), but were attenuated substantially when adjusted for the contextual variables (i.e., Model 3). In the case of all-cause mortality, however, estimates remained essentially unchanged across all three levels of model adjustment.

Risks of increased COVID-19 incidence and hospitalizations using Model 3 were strongest with exposure to NO_2 (i.e., HRs and 95% confidence intervals (CIs): 1.18 [1.14–1.23] and 1.19 [1.12–1.27], respectively), but risk of COVID-19 mortality was strongest with exposure to $PM_{2.5}$ (i.e., HR and 95% CI: 1.23 [1.04–1.44]; Commentary Figure).

Andersen and colleagues also compared COVID-19 deaths with deaths from all causes. They reported elevated risk of all-cause mortality associated with exposures to $PM_{2.5}$, BC, and NO_2 (Commentary Figure). Deaths from COVID-19



Commentary Figure. Associations between estimated annual average pollutant concentrations and mortality among cohort participants. Data shown are hazard ratios and 95% confidence intervals estimated per interquartile range increases in 1-year mean exposure, namely: 0.55 µg/m^3 for $PM_{2.5}$, 1.14 µg/m^3 for PM_{10}, 0.09 µg/m^3 for BC, 3.49 µg/m^3 for NO_2, and 2.79 µg/m^3 for O_3. Results are from the analyses using all available individual- and contextual-level variables (Model 3). (Source: Investigators' Report Table 3.)

associated with PM and NO_2 were much higher than those from all causes.

Results of Additional Analyses

Analyses with the exposure estimates from the ELAPSE model showed strong and significantly positive associations with all COVID-19 outcomes and with all-cause mortality and were comparable to those observed with the main exposure model.

The investigators found no associations during the first wave of the pandemic but found significant and positive associations between $PM_{2.5}$, BC, and NO_2 and all three COVID-19 outcomes during the second wave when the number of cases, hospitalizations, and deaths were much higher.

One of the aims of the study was to identify whether any subgroup of the population was more susceptible to air pollution–related COVID-19 incidence. Here, they found that those aged 65 years and older experienced greater risks associated with NO_2 exposure (compared to younger people) and those of lower SES (according to several indicators) had greater risks associated with both NO_2 and $PM_{2.5}$ exposures (compared to those of higher SES). The investigators also reported greater risks for COVID-19 incidence with $PM_{2.5}$ and NO_2 exposures among those who had pre-existing cardiovascular and respiratory disease comorbidities and among individuals who had dementia and diabetes, although not all of these differences were statistically significant.

In analyses restricted to individuals who tested positive for COVID-19, they found that exposures to $PM_{2.5}$ and NO_2 were associated with increased risks of hospitalizations (i.e., HRs 1.04 [CI: 1.01–1.08] and 1.06 [CI: 1.10–1.12], respectively), but no association was observed with the other pollutants. The risks in this subgroup were notably smaller than those reported with the full cohort (see Commentary Figure: HRs 1.09 [CI: 1.01–1.17] and 1.19 [CI: 1.12–1.27], respectively). In this same subgroup, PM_{10} was inversely associated with risk of COVID-19 mortality, but all other pollutants were unrelated to this outcome.

The exposure–response functions were linear or curvilinear for the majority of the pollutants and COVID-19 outcomes. Finally, analyses using two-pollutants models showed that associations, especially for $PM_{2.5}$ adjusted for NO_2 and O_3, were attenuated substantially. Associations with PM_{10} were the most robust to adjustment for other pollutants.

HEI REVIEW COMMITTEE'S EVALUATION

EVALUATION OF STUDY DESIGN, DATASETS, AND EPIDEMIOLOGICAL APPROACHES

This study represents an important contribution to our knowledge about potential associations between long-term exposure to air pollution and COVD-19–related health outcomes. Major strengths of the study design were the inclusion of the full Danish population and the rigorous adjustments for individual- and contextual-level SES characteristics. The report presented estimates of risks for three COVID-19–related outcomes associated with exposures to five pollutants (i.e., $PM_{2.5}$, PM_{10}, BC, NO_2, and O_3) and found increased risks associated with all but O_3. 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.

In its independent evaluation of the Investigators' Report, the HEI Review Committee agreed that the study documents that long-term exposures to ambient air pollution appear to be associated with adverse COVID-19 morbidity and mortality among Danish adults. A noted strength of this study is that during the second wave of the pandemic, in particular, the investigators were able to capture nearly all cases, as testing was widely available for free in Denmark during this period. The Committee was also impressed with the use of high-resolution exposure estimates for the five pollutants. They thought that the exposure models used and the methods of assigning exposure estimates to cohort participants were appropriate for these analyses.

Another strength of the study was that the investigators had access to participants' residential addresses for estimating exposures, whereas many other epidemiological studies based on administrative data have used the less precise approach of using the location of participant residential ZIP codes or postal codes. Their ability to adjust for municipality-level access to healthcare and municipality-level monthly COVID-19 positivity rates (as a proxy for spatial and temporal pandemic development) was another important characteristic of the study design.

The Committee liked that Andersen and colleagues were very thorough in their analyses and conducted many sensitivity analyses, some of which are not included in this summary. The Committee was impressed with their efforts at examining the effects of different levels and combinations of covariate adjustment, testing for effect modification by numerous individual-level characteristics, evaluating two different sources of exposure predictions and multipollutant models, and comparing their results between pandemic waves and among those who had tested positive for COVID-19 separately.

The Committee agrees with the investigators that there are many challenges to measuring cases of COVID-19 incidence, hospitalization, and death accurately. As described earlier, here, the investigators defined incidence as having a first positive PCR test and COVID-19 hospitalization as having been admitted within 14 days of the first positive PCR test. The Committee notes that the accuracy of these data necessarily depends on voluntary participation in testing, testing capacity, accessibility, cost, and accuracy, among other challenges, all of which are likely to vary across Denmark and throughout the course of the pandemic. That is, under-ascertainment of outcomes and variability of under-ascertainment across the country are potential sources of bias. For example, bias would be introduced if those living in urban areas, where pollution levels would be greatest, had better access to testing than those living in areas where pollution levels are lower. Potential differential ascertainment in COVID-19 outcomes also has implications for the subgroup analyses identifying susceptible populations because some subgroups (e.g., perhaps those of higher SES) might have had better access to testing. In the second wave of the pandemic, however, PCR tests were widely and freely available to all, making it therefore easier to ascertain cases. We would therefore expect to have less bias related to case ascertainment in the analyses restricted to the second wave of the pandemic as compared to the other analyses.

The investigators defined COVID-19 deaths as death from any cause within 30 days of the detection of a COVID-19 infection, as confirmed by PCR test. That definition also presents challenges to accuracy because those who are hospitalized for any reason are more likely to be tested for COVID-19 (than asymptomatic members of the general public) and are also more likely to die from other, non–COVID-19 causes. For example, someone admitted to hospital following a heart attack could also test positive for COVID-19 upon admission and later die because of heart failure; however, according to this case definition, their death would be attributed to COVID-19 (i.e., spuriously linking air pollution and a COVID-19 death). Thus, the outcomes defined in this way likely capture a substantial number of hospitalizations and deaths that were not related to COVID-19. Additionally, those who did in fact die of COVID-19 more than 30 days after the initial diagnosis would not be included in this group.

Despite controlling for many individual- and contextual-level indicators of SES in their epidemiological models, the investigators were unable to control for some characteristics relevant for studying COVID-19, such as personal and local patterns of adherence to public health measures (e.g., social distancing and wearing of face masks). Some or all of these could be related to patterns of pollution, and lack of adjustment for them could therefore be a source of bias. Additionally, there might be differential associations according to different COVID-19 strains that were not captured in the analyses.

Overall, however, the Committee was impressed with the quality of the epidemiological datasets, general analytic approaches, and in particular the large number of sensitivity analyses explored, although there were some important limitations to them.

DISCUSSION OF THE FINDINGS AND INTERPRETATION

Generally, the Committee found that the report presented a balanced and accurate presentation and interpretation of the study results. Some of the findings, however, remained somewhat unexplained and difficult to interpret, including the very elevated estimates of risk in many cases. For example, the investigators reported that an increase in exposure to $PM_{2.5}$ of only 0.5 µg/m^3 was associated with an HR of 1.10 for COVID-19 incidence and an HR of 1.23 for COVID-19 mortality. For context, a recent systematic review and meta-analysis of 71 cohort studies on long-term exposure to $PM_{2.5}$ and mortality reported an HR of only 1.08 for all-cause mortality per 10 µg/m^3 (Chen and Hoek 2020), and the ELAPSE pooled analysis of eight European cohorts reported an HR 1.28 for all-cause mortality per 10 µg/m^3 for $PM_{2.5}$ (Strak et al. 2021). It is worth noting here that the mean exposures to pollutants in this study were relatively low and had limited variability in some cases, which make it difficult to compare with findings from locations where exposures are higher or have greater ranges. Regardless, the estimates of risk for mortality reported by Andersen and colleagues are much greater than those observed elsewhere and suggest that there might be important unaccounted sources of bias in the study although the source of bias was not readily apparent.

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). This finding could suggest that air pollution is acting more on the development of disease than on its progression, yet in the full population, associations were much stronger for COVID-19 mortality than incidence or hospitalization. As such, it is possible that there remained bias due to who was getting infected or tested. Similarly, the investigators showed that controlling for municipality-level monthly COVID-19 positivity rates did not affect their results, whereas one might have expected that to have attenuated the associations. The fact that associations between air pollution exposures and COVID-19 were limited to the second wave could be because the more limited testing in the first wave made it more difficult to detect associations, or it could be related to differences in the virus strains in the two waves.

In addition to the very strong associations reported with $PM_{2.5}$, the inverse associations between exposure to O_3 and the various outcomes are difficult to explain. The inverse associations between several health outcomes and O_3, however, are generally consistent with several other recent European studies (e.g., Stafoggia et al. 2022; Strak et al. 2021; Veronesi et al. 2022). It is possible that this finding reflects atmospheric chemistry in the environment under which ozone reacts with other pollutants to form new unmeasured but toxic components.

For the other pollutants, Andersen and colleagues observed that the risks for COVID-19 incidence and hospitalizations were both highest with exposures to NO_2. NO_2 is often considered a marker of locally varying, traffic-related air pollution, as compared to $PM_{2.5}$, which might better represent regional variation in air quality arising from non–traffic-related sources. As such, these findings might reflect the biological importance of traffic-related pollution for these relationships or might have captured part of the population that showed more movement in and out of their homes and thus were exposed to more opportunities for disease transmission. Collectively, these findings add to a somewhat inconclusive literature on this topic. One recent systematic review by Hernandez Carballo and colleagues (Hernandez Carballo et al. 2022) summarized findings from 116 studies that report 355 combinations of different pollutant-COVID-19 outcomes and found that only about half of those on incidence or mortality reported statistically significant increased risks associated with exposure. Among those that did find positive associations, incidence was associated most strongly with exposures to $PM_{2.5}$, PM_{10}, NO_2, O_3, and carbon monoxide, whereas COVID-19 deaths were associated most strongly with $PM_{2.5}$ and NO_2. Notably, Hernandez Carballo and colleagues concluded that most studies included in the review exhibited high risk of confounding and outcome measurement bias. A separate systematic review and meta-analysis (Sheppard et al. 2023) severity, and deaths. However, such studies are unable to account for individual-level differences in major confounders like socioeconomic status and often rely on imprecise measures of $PM_{2.5}$ reported that a 10-μg/m^3 increase in $PM_{2.5}$ was associated with a 1.66 (95% CI: 1.31–2.11) increased odds of COVID-19 infection (N = 7) and a 1.40 increased odds of mortality (N = 5), both of which are much lower than the equivalent risks of 6.04 and 49.70 reported here. Evidence from the rapidly expanding literature on this topic therefore remains mixed, both in terms of findings and in quality of study designs.

CONCLUSIONS

In summary, this study represents an important contribution to our knowledge about potential associations between long-term exposure to air pollution and COVD-19–related health outcomes. The study design is a great improvement over others in the currently available literature on this topic due to the more complete capture of cases and the rigorous adjustments for individual- and contextual-level SES characteristics.

The report demonstrated large, elevated risks for three different COVID-19–related outcomes associated with exposures to four pollutants (i.e., $PM_{2.5}$, PM_{10}, BC, and NO_2). These findings were largely robust to sensitivity analyses although some differences between waves of the pandemic, lower risks among those with COVID-19 diagnoses, and the very large effect sizes leave some concerns about residual bias.

This is one of the first cohort studies and the first study funded by HEI to investigate the association between air pollution and COVID-19. The rich epidemiological datasets used, which included many individual-level characteristics for all adults in Denmark, allowed the investigators to address some of the major limitations of previous ecological studies on this topic. Limitations remained, however, regarding how the outcomes were defined and measured and the inability to control several pandemic-related issues, including adherence to public health guidelines. Ultimately, this study has documented that long-term exposures to ambient air pollution do appear to be associated with adverse COVID-19 morbidity and mortality among Danish adults.

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ABBREVIATIONS AND OTHER ITEMS

AIRCODEN	Long-term exposure to AIR pollution and COvid-19 mortality and morbidity in DENmark: who is most susceptible?
BC	black carbon
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus diseases 2019
DEHM	Danish Eulerian Hemispheric Model
DKK	Danish krone (currency)
EC	elemental carbon
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Air Pollution Effects
HEI	Health Effects Institute
HR	hazard ratio
ICD	International Classification of Diseases
IQR	interquartile range
LUR	land use regression
NO_2	nitrogen dioxide
O_3	ozone
OR	odds ratio
PCR	polymerase chain reaction
PM	particulate matter
$PM_{2.5}$	particulate matter with an aerodynamic diameter <2.5 µm
PM_{10}	particulate matter with an aerodynamic diameter <10 µm
RR	rate ratio
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SES	socioeconomic status
UBM	urban background model
WHO	World Health Organization

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