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

Zorana Jovanovic Andersen, Jiawei Zhang, Youn-Hee Lim, Rina So, Jeanette T. Jørgensen, Laust H. Mortensen, George M. Napolitano, Thomas Cole-Hunter, Steffen Loft, Samir Bhatt, Gerard Hoek, Bert Brunekreef, Rudi G.J. Westendorp, Matthias Ketzel, Jørgen Brandt, Theis Lange, Thea Kølsen Fischer

Includes a Commentary by the Institute's Review Committee

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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.

ABOUT THIS REPORT

Research Report 214, *Long-Term Exposure to AIR Pollution and COVID-19 Mortality and Morbidity in DENmark: Who Is Most Susceptible? (AIRCODEN),* presents a research project funded by the Health Effects Institute and conducted by Dr. Zorana Jovanovic Andersen of the University of Copenhagen, Denmark, and her colleagues. The report contains three main sections:

The **HEI Statement**, prepared by staff at HEI, is a brief, nontechnical summary of the study and its findings; it also briefly describes the Review Committee's comments on the study.

The **Investigators' Report**, prepared by Andersen and colleagues, describes the scientific background, aims, methods, results, and conclusions of the study.

The **Commentary**, prepared by members of the Review Committee with the assistance of HEI staff, places the study in a broader scientific context, points out its strengths and limitations, and discusses the remaining uncertainties and implications of the study's findings for public health and future research.

This report has gone through HEI's rigorous review process. When an HEI-funded study is completed, the investigators submit a draft final report presenting the background and results of the study. This draft report is first examined by outside technical reviewers and a biostatistician. The report and the reviewers' comments are then evaluated by members of the Review Committee, an independent panel of distinguished scientists who are not involved in selecting or overseeing HEI studies. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, as necessary, to revise their report. The Commentary reflects the information provided in the final version of the report.

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PREFACE

HEI's Program on Air Pollution, COVID-19, and Human Health

INTRODUCTION

On January 20, 2020, the U.S. Centers for Disease Control and Prevention (CDC) confirmed the first case of COVID-19 in the United States. On March 20, after more than 118,000 cases in 114 countries and 4,291 deaths, the World Health Organization (WHO) declared a global COVID-19 pandemic, and countries around the world began instituting preventive measures (e.g., lockdowns) to slow the spread of disease. The closing of nonessential businesses in many locations around the world led to reduced emissions of air pollutants from the energy sector and other industries and significantly reduced traffic volumes due to stay-at-home policies.

Although there has been an enormous cost to this pandemic, both human and economic, it created unprecedented conditions that lent themselves to timely and novel air pollution research aimed at exploring policy-relevant topics, including key factors that contributed to changing patterns of air pollution over space and time, potential benefits to human health associated with such changes in exposures, and relationships between past or current exposures to air pollution and susceptibility to the effects of COVID-19 infections (Boogaard et al. 2021).

Because of known associations between air pollution and respiratory hospitalizations and mortality, researchers quickly initiated investigations into potential links between air pollution exposure and COVID-19 (Wu et al. 2020; Liang et al. 2020). There were many unique challenges to this task because the context within which we study associations between air pollution and health was altered due to widespread changes to daily life related to the pandemic (e.g., changes in emission sources, behaviors that affect exposures, and healthcare access and use). Furthermore, COVID-19 outcomes are difficult to study due to various factors, including initial lack of testing, inconsistency in diagnoses, and healthcare systems being overloaded. COVID-19 incidence data — and to a lesser extent mortality data — have also been underestimated in all countries, thus affecting all analyses (Copat et al. 2020). Moreover, the spread of the disease has been shown to be highly dynamic both in time and space. Most transmission has been caused by a few superspreading events influenced by human behavior, socioeconomic and demographic factors (e.g., household size and multigeneration households), and compliance with control measures (Chang et al. 2021, Samet et al. 2021).

In May 2020, only 2 months after the WHO declared the COVID-19 outbreak a global pandemic, HEI issued RFA 20-1B that sought to fund studies to investigate potential associations between air pollution, COVID-19, and human health. HEI formulated specific research objectives where it expected to make a valuable contribution to this rapidly expanding new field of research. HEI was interested in applications for studies designed specifically to address the following questions on this topic:

1. **Accountability Research:** What are the effects of the unprecedented interventions implemented to control the COVID-19 pandemic on emissions, air pollution exposures, and human health? Emerging evidence suggested that changes in economic activity and human mobility following government restrictions led to noticeable reductions in pollutant emissions and pollutant concentrations in ambient air — in particular, nitrogen dioxide (NO_2) — in many cities around the world (Ogen 2020; Schiermeier 2020; Zhang et al. 2020).

The observed changes in air quality presented a unique opportunity for accountability research on this "natural experiment." HEI acknowledged that it could be difficult for investigators to find control populations not affected by the interventions; in addition, interventions in various locations occurred during different periods. Moreover, there would be challenges related to the major reorientating of healthcare systems to deal with COVID-19 and accompanying challenges in estimating comparable hospitalization rates and other health outcomes at a time when utilization of healthcare was changed and diagnostic criteria for COVID-19 and respiratory outcomes were also variable across time and space. Studies investigating health effects are needed to account for those kinds of changes.

2. **Susceptibility Factors:** Are individuals or populations who have been chronically or acutely exposed to higher levels of air pollution at greater risk of mortality from COVID-19 compared to those exposed to lower levels of air pollution? Do the potential effects differ by race or ethnicity or by measures of socioeconomic status?

   Limited evidence from the 2002–2004 SARS outbreak indicated a possible association between higher air pollution concentrations and higher-than-expected death rates (Cui et al. 2003; Kan et al. 2005). Early evidence suggested that individuals with existing comorbidities (e.g., diabetes, high blood pressure, or heart and lung diseases) might be more susceptible to the effects of a COVID-19 infection and at higher risk of mortality from COVID-19 (Wang et al. 2020; Yang et al. 2020). There was also evidence that racial and socioeconomic disparities might lead to higher observed risks (Brandt et al. 2020).

   Because exposure to air pollution is also known to contribute to the development of such underlying diseases (Cohen et al. 2017; HEI 2019), air pollution might also increase susceptibility to morbidity and mortality from COVID-19, possibly in ways that we do not fully understand (Conticini et al. 2020).

STUDY SELECTION

HEI established an independent Panel of outside experts to review all applications submitted in response to the RFA. The HEI Research Committee reviewed the Panel's suggestions and recommended five studies for funding to HEI's Board of Directors, which approved funding in December 2020. Members of the Research Committee with any conflict of interest were recused from all discussions and from the decision-making process. This Preface summarizes the five studies, HEI's oversight process, and the review process for the final reports.

OVERVIEW OF THE AIR POLLUTION, COVID-19, AND HUMAN HEALTH STUDIES

HEI expected to make a valuable contribution to this rapidly expanding new field of research with the five studies funded under RFA 20-1B (**Preface Table**).

Zorana Andersen of the University of Copenhagen and colleagues proposed to use a population-based nationwide cohort of 3.7 million 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, ethnicity, and comorbidities.

Kai Chen of Yale University and colleagues proposed to assess the impact of ambient air pollution reduction on mortality during COVID-19 lockdowns in four countries (Germany, Italy, China, and the United States). First, they proposed to evaluate whether changes in mortality are associated with changes in concentrations of NO_2 and $PM_{2.5}$ before, during, and after the lockdown (study period 2015–2020). Next, they proposed to disentangle the short-term effects of NO_2 versus $PM_{2.5}$ on mortality.

Michael Kleeman of the University of California–Davis and colleagues proposed to evaluate the chronic and acute effects of air pollution exposure on COVID-19 incidence, mortality, and long-term complications among the approximately 10 million residents of 432 health neighborhoods in Los Angeles, California. First, they planned to use chemical transport and land use regression models to develop chronic and acute daily $PM_{2.5}$, NO_2, and O_3 exposure estimates at multiple spatial resolutions. They then proposed to assess the association between exposure and COVID-19 incidence and mortality between March 16 and September 4, 2020, and with new and exacerbated long-term COVID-19 complications up to 18 months following initial infection.

Jeanette Stingone of Columbia University and colleagues proposed to evaluate the interactions between chronic air pollution exposure and neighborhood vulnerability in relation to adverse COVID-19 outcomes in New York City. They first would use electronic health record data with more than 37,000 COVID-19 patients from five large hospital systems to evaluate single and multipollutant air pollution exposures in relation to COVID-19 hospitalization, inpatient length of stay, ICU

Preface Table. HEI's Research Program on Air Pollution, Covid-19, and Human Health

Investigator (institution)	Study Title	Location	Study Design and Population	Theme	Final Report Published
Zorana Andersen (University of Copenhagen)	Long-Term Exposure to Air Pollution and COVID-19 Mortality and Morbidity in Denmark: Who Is Most Susceptible?	Denmark	Cohort Study: Population-based nation-wide cohort of all Danes aged 40 years or older (*N* > 3 million)	Susceptibility	HEI Report 214, 2023
Kai Chen (Yale University)	Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdown: A Natural Experience Study	China, Germany, Italy, and the United States	Time Series Study: Populations in 4 countries: China (Jiangsu Province), Italy, Germany, and the U.S. (California)	Accountability	Expected Summer 2024
Michael Kleeman (University of California–Davis)	Ambient Air Pollution and COVID-19 in California	California, United States	Cohort Study: Population-based cohort using a medical records database in Southern California from Kaiser Permanente	Susceptibility	Expected Summer 2024
Jeanette Stingone (Columbia University)	Race, Ethnicity, and Air Pollution in COVID-19 Hospitalization Outcomes (REACH OUT Study)	New York City, United States	Cohort Study: Population-based cohort using harmonized electronic health records in NYC	Susceptibility	Expected Winter 2024
Cathryn Tonne (ISGlobal)	Air Pollution in Relation to COVID-19 Morbidity and Mortality: A Large Population-Based Cohort Study in Catalonia, Spain	Catalonia, Spain	Cohort Study: Population-based region-wide cohort of 6 million residents of Catalonia, Spain	Susceptibility	Expected Winter 2024

admission, ventilator use, and death. Then they would complete a validation study, sampling all patients from four of the hospital systems to ensure the quality of harmonized data.

Cathryn Tonne of ISGlobal and colleagues proposed to assess whether long-term exposure to air pollution increases the risk of COVID-19 hospitalization and mortality in the general population of 5 million people in Catalonia, Spain, and whether short-term exposure to air pollution increases the risk of COVID-19 hospitalization and mortality among the 300,000 people who tested positive for SARS-COV-2 during the study period.

STUDY OVERSIGHT AND REVIEW OF FINAL REPORTS

Members of HEI's Research Committee provided advice and feedback on the study designs, analytical plans, and study progress throughout the duration of the research program. Each study team submitted biannual progress reports. The studies were subject to HEI's special quality assurance procedures that included an audit by an independent audit team (see *www.healtheffects.org/research/quality-assurance*). The five studies commenced in Spring 2021 and final reports are expected to be pub-

lished in 2023 and 2024. HEI is planning to publish an overall summary and interpretation of the COVID-19 research program once all studies have been reviewed.

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HEI STATEMENT

Synopsis of Research Report 214

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 <2.5 μg/m^3 in diameter, coarse particulate matter <10 μg/m^3 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 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.

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 hospi-

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.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Zorana J. Andersen at the University of Copenhagen, Denmark, and colleagues. Research Report 214 contains both the detailed Investigators' Report and a Commentary on the study prepared by the Institute's Review Committee. **ANDERSEN 214**

talization 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 μg/m^3 for fine particulate matter, 12.7 μg/m^3 for coarse particulate matter, 0.3 μg/m^3 for black carbon, 10.7 μg/m^3 for nitrogen dioxide, and 54.5 μg/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 μg/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 μg/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.

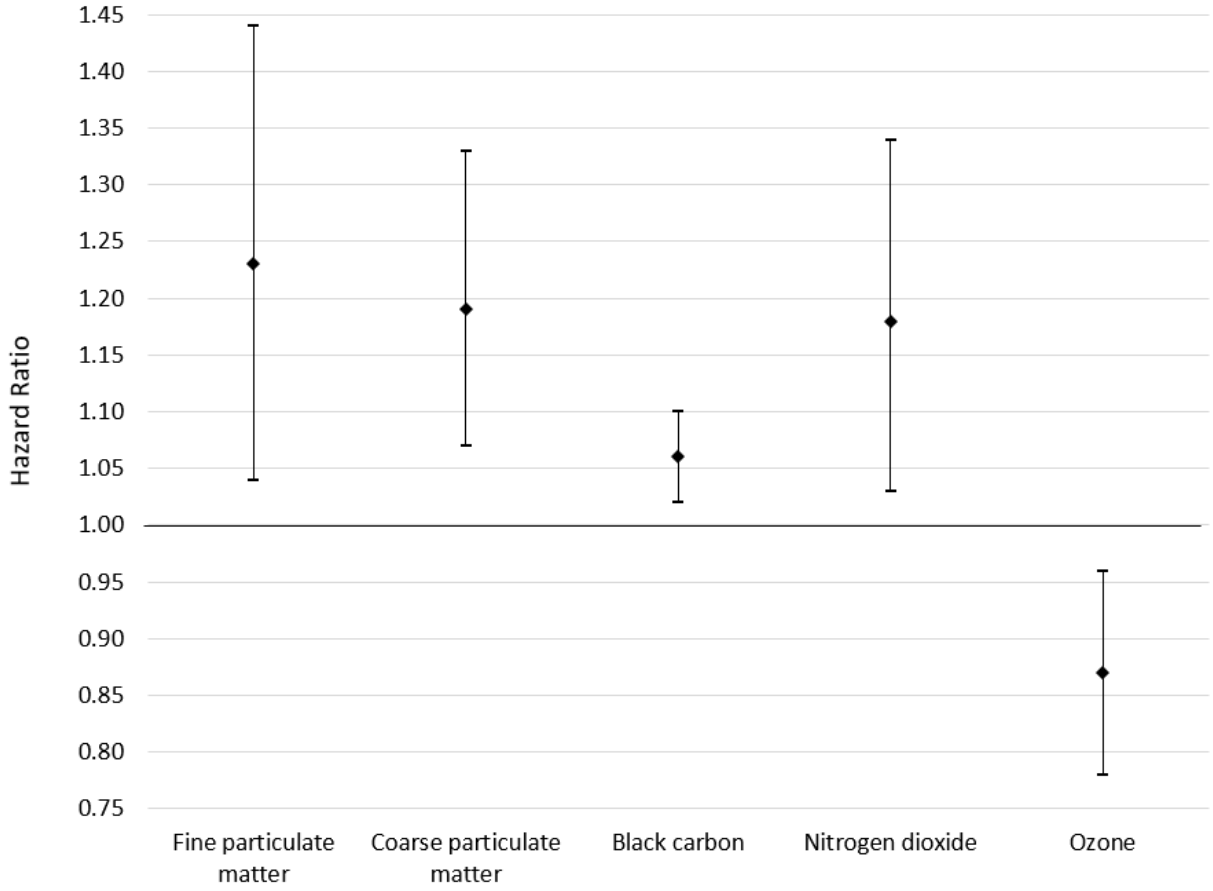
INTERPRETATION AND CONCLUSIONS

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 COVD-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.



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 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. (Source: Investigators' Report Table 3).

INVESTIGATORS' REPORT

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

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ABSTRACT

Introduction Early ecological studies have suggested a link between air pollution and Coronavirus Diseases 2019 (COVID-19*); however, the evidence from individual-level prospective cohort studies is still sparse. Here, we have examined, in a general population, whether long-term exposure to air pollution is associated with the risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and developing severe COVID-19, resulting in hospitalization or death and who is most susceptible. We also examined whether long-term exposure to air pollution is associated with hospitalization or death due to COVID-19 in those who have tested positive for SARS-CoV-2.

Methods We included all Danish residents 30 years or older who resided in Denmark on March 1, 2020. and followed them in the National COVID-19 Surveillance System until first positive test (incidence), COVID-19 hospitalization, or death until April 26, 2021. We estimated mean levels of nitrogen dioxide (NO_2), particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$), black carbon (BC), and ozone (O_3) at cohort participants' residence in 2019 by the Danish Eulerian Hemispheric Model/Urban Background Model. We used Cox proportional hazard models to estimate the associations of air pollutants with COVID-19 incidence, hospitalization, and mortality adjusting for age, sex, and socioeconomic status (SES) at the individual and area levels. We examined effect modification by age, sex, SES (education, income, wealth, employment), and comorbidities with cardiovascular disease, respiratory disease, acute lower respiratory infections, diabetes, lung cancer, and dementia. We used logistic regression to examine association of air pollutants with COVID-19–related hospitalization or death among SARS-CoV-2 positive patients, adjusting for age, sex, individual- and area-level SES.

Results Of 3,721,810 people, 138,742 were infected, 11,270 hospitalized, and 2,557 died from COVID-19 during 14 months of follow-up. We detected strong positive associations with COVID-19 incidence, with hazard ratio (HR) and 95% confidence interval (CI) of 1.10 (CI: 1.05–1.14) per 0.5-µg/m^3 increase in $PM_{2.5}$ and 1.18 (CI: 1.14–1.23) per 3.6-µg/m^3 increase in NO_2. For COVID-19 hospitalizations and for COVID-19 deaths, corresponding HRs and 95% CIs were 1.09 (CI: 1.01–1.17) and 1.19 (CI: 1.12–1.27), respectively for $PM_{2.5}$, and 1.23 (CI: 1.04–1.44) and 1.18 (CI: 1.03–1.34), respectively for NO_2. We also found strong positive and statistically significant associations with BC and negative associations with O_3. Associations were strongest in those aged 65 years old or older, participants with the lowest SES, and patients with chronic cardiovascular, respiratory, metabolic, lung cancer, and neurodegenerative disease. Among 138,742 individuals who have tested positive for SARS-Cov-2, we detected positive association with COVID-19 hospitalizations (N = 11,270) with odds ratio and 95% CI of 1.04 (CI: 1.01–1.08) per 0.5-µg/m^3 increase in $PM_{2.5}$ and 1.06 (CI: 1.01–1.12) per 3.6-µg/m^3 increase in NO_2, but no association with PM with an aerodynamic diameter <10 µm (PM_{10}), BC, or O_3, and no association between any of the pollutants and COVID-19 mortality (N = 2,557).

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

Conclusions This large nationwide study provides strong new evidence in support of association between long-term exposure to air pollution and COVID-19.

INTRODUCTION

One of the important public health objectives in the midst of COVID-19 epidemic was to identify key modifiable factors that could contribute to increased risk of contracting the SARS-CoV-2 and developing COVID-19 or worsen the severity of the health outcomes among individuals with COVID-19. These factors are crucial for the management of the current COVID-19 pandemic and preparation of strategies for future similar pandemics. Air pollution is the major environmental stressor and is the fourth top ranked global risk factor for morbidity and mortality (after smoking, high blood pressure, and poor diet). It caused 6.7 million deaths in 2019, from ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, acute lower respiratory infections, lung cancer, diabetes, and neonatal deaths (HEI 2020).

AIR POLLUTION AND COVID-19: IS THERE A BIOLOGICAL PLAUSIBILITY?

Several biologically plausible mechanisms and pathways may explain how long-term exposure to particulate matter (PM) and gaseous pollutants may increase risk of COVID-19. Long-term exposure to air pollution may worsen COVID-19 severity and lethality indirectly, by increasing the risk of respiratory, cardiovascular, and metabolic diseases as well as lung cancer (HEI 2020), which in turn increase the risk of severe disease and death from COVID-19 (Atkins et al. 2020; Elliott et al. 2021; Veronesi et al. 2022; Williamson et al. 2020).

Experimental studies show that PM exposure can also directly increase vulnerability to the SARS-CoV-2 and other respiratory infections by impairing cell immunity and weakening host defense mechanisms, and thus increasing susceptibility to respiratory infections (Woodby et al. 2021). This increased vulnerability is caused by direct cellular damage and indirectly via oxidative stress and inflammation in the lung and system, which can increase viral spread, enhance virus-induced tissue damage and inflammation, promoting dysfunction of a variety of organs, including the lungs, heart, kidney, and brain, resulting in more severe COVID-19 or death (Woodby et al. 2021).

Furthermore, the plausibility of the link between air pollution and COVID-19 is supported by the likely link between air pollution with other respiratory infections, such as pneumonia. Only a few studies have examined associations between long-term exposure to air pollution and pneumonia incidence or hospitalizations (Carey et al. 2016; Neupane at el. 2010; Salimi et al. 2018), with mixed results, as two reported positive associations (Carey et al. 2016; Neupane at el. 2010) and one found no association (Salimi et al. 2018). Based on these three studies, recent systematic review and meta-analyses from the Health Effects Institute (HEI) on the associations between traffic-related air pollution (including NO_2, $PM_{2.5}$, and elemental carbon [EC]) and a number of health outcomes, we have concluded that the confidence was very low or low for an association with traffic-related air pollution and the risk of acute lower respiratory infections (Boogaard et al. 2020). However, the Global Burden of Disease study has recognized the causal link between air pollution and acute lower respiratory infection mortality (HEI 2022), which is supported by solid evidence from 13 studies on air pollution and pneumonia mortality (Bowe et al. 2019; Carey et al. 2013; Jerrett 2022; Katanoda et al. 2011; Kazemiparkouhi et al. 2020; Lim et al. 2019; Liu et al. 2022; Pinault et al. 2017; Pope et al. 2004, 2019; Turner et al. 2016; Yang et al. 2018; Yorifuji et al. 2013) of which all but one (Carey et al. 2013) detected associations.

EARLY RESEARCH ON LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19: CORRELATION AND ECOLOGICAL STUDIES

Early correlation and ecological studies have raised headlines suggesting that air pollution may increase the risk of COVID-19, despite the fallacies of such designs (Villeneuve and Goldberg 2020). A study in the United States gained instant attention by the media in May 2020, when preliminary (non–peer-reviewed) results by Wu and colleagues (Wu et al. 2020) showed that even a small increase of 1 $\mu g/m^3$ in long-term exposure to $PM_{2.5}$ led to a large 20% increase in the COVID-19 death rate, with the magnitude of increase 20 times that observed for $PM_{2.5}$ and all-cause mortality (Di et al. 2017). This impressive estimate later attenuated to 8%, after adjustment for the timing of social distancing policies and the population's age distribution. However, this study was criticized for possibly grossly overestimating the effect of air pollution on COVID-19 mortality for several reasons. The major issue is the ecological design, where mortality rates in 3,080 U.S. counties were compared against very crude, county-average concentrations of $PM_{2.5}$ over a 17-year period, and lacked individual-level data on exposure, outcome, and important confounders (SES, lifestyle, and comorbidities). The majority of early studies on long-term exposure to air pollution and COVID-19 used ecological designs, which have typically linked mean air pollution levels over an area (county, municipality, postal code areas, region, etc.) to the COVID-19 death or COVID-19 case-fatality rates in that area.

Here we give examples of results from selected studies (Liang et al. 2020; Travaglio et al. 2021) to illustrate inconsistencies in findings from the same areas or countries and to call for careful interpretation of these early results. Following Wu and colleagues, another nationwide U.S. study, based on the same county-level data as the study by Wu and colleagues but utilizing a different air pollution modeling approach, examined the long-term effect of NO_2, $PM_{2.5,}$ and O_3 on COVID-19 case fatality and mortality rates. They reported increases of 7.1% (CI: 1.2%–13.4%) and 11.2% (CI: 3.4%–19.5%) per

4.5-ppb increase in NO_2 for case fatality and mortality rate, respectively (Liang et al. 2020). Notably, in contrast to Wu and colleagues, Liang and colleagues reported no association with $PM_{2.5}$. Similarly, two ecological studies from England on long-term exposure to air pollution and COVID-19 mortality show somewhat conflicting results, notably using the different spatial units for analyses and different statistical approaches. A study based on COVID-19 deaths up to June 30, 2020 aggregated in Lower Layer Super Output Area spatial units (N = 32,844) found a 0.5% (95% credible interval: –0.2%–1.2%) and 1.4% (CI: –2.1%–5.1%) increase in the COVID-19 mortality rate for every 1-μg/m^3 increase in NO_2 and $PM_{2.5}$, respectively (Konstantinoudis et al. 2021). On the other hand, Travaglio and colleagues reported a significant association between long-term exposure to NO_2 and O_3 and COVID-19 deaths at the regional level (Lower Tier Local Authorities), and none with $PM_{2.5}$ (Travaglio et al. 2021).

In summary, early evidence based on long-term exposure to air pollution and susceptibility to COVID-19 is limited by ecological study design, for which estimates cannot be used to make inferences on individual-level risk, resulting in the ecological fallacy (Villeneuve and Goldberg 2020). Individual-level data are needed to provide valid inference in understanding the impact of air pollution on contracting the SARS-CoV-2 and the development of the COVID-19 disease. Notably, many of the aforementioned studies have been published ahead of peer review, calling for extra caution when drawing inference from these early results, as pointed out in an editorial (Heederik et al. 2020).

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19: CORRELATION AND ECOLOGICAL STUDIES

Epidemiological evidence based on the cohort studies with individual-level data on long-term exposure to air pollution and later onset of COVID-19 is still very sparse and mixed. Travaglio and colleagues, as the first at that time, used individual-level data on "infectivity" from the UK Biobank, where of the 1,450 tested individuals 699 tested positive for SARS-CoV-2 and found that a single-unit increase in $PM_{2.5}$ levels was associated with a statistically significant 12% increase in COVID-19 cases in contrast to their above mentioned results on regional analyses (Travaglio et al. 2021). Only three studies examined association of long-term exposure to air pollution to COVID-19 incidence in the general population, where incidence was defined as the first positive SARS-CoV-2 test, and they offer mixed results. In a city-wide study of 62,848 residents of Varese, Italy, of whom 4,408 tested positive for COVID-19 in first year of the pandemic, Veronesi and colleagues detected increases of 5.1%, 2%, and 4% in COVID-19 rates for each μg/m^3 increase in $PM_{2.5}$, NO_2, and PM_{10}, respectively (Veronesi et al. 2022). In 424,721 subjects from UK Biobank, of whom 10,790 tested positive between March 16 and December 31, 2020, Sheridan and colleagues detected associations with odds ratios (ORs) of 1.06 and 1.05 for COVID-19 incidence for each 1.3- and 9.9-μg/m^3 increase in $PM_{2.5}$ and NO_2, respectively, but found no associations with PM_{10}, and no association of any pollutants with COVID-19 hospitalizations (N = 1,598) or deaths (N = 568) (Sheridan et al. 2022). In 1,594,308 subjects from Rome, of whom 79,976 tested positive and 2,656 died from COVID-19 between January 1, 2020, and April 15, 2021, Nobile and colleagues on the other hand, found no associations with COVID-19 incidence, but reported 8% and 9% higher risk of dying from COVID-19 for each 0.92- and 9.22-μg/m^3 increase in $PM_{2.5}$ and NO_2, respectively (they had no data on PM_{10}) (Nobile et al. 2022). In a slightly different approach, a study by Kogevinas and colleagues, which was based on 9,605 subjects from the COVID-19 cohort of Catalonia (COVICAT) study in Barcelona who provided detailed questionnaire data on COVID-19 and of whom 481 (5%) had COVID-19, reported associations with $PM_{2.5}$ and NO_2, but none with BC. In a subset of 4,103 subjects who provided blood samples, they found no association of air pollution with positive antibodies for SARS-CoV-2 (mix of incidence and prevalence), but also here, detected associations with incidence based on self-reported COVID-19. Kogevinas and colleagues have notably reported stronger associations with air pollution with increasing severity of COVID-19 outcome, in terms of COVID-19 severe symptoms, hospitalization, or death (Kogevinas et al. 2021).

Four studies, all from North America, which had access to data only on those who tested positive for COVID-19, examined whether long-term exposure to air pollution affects COVID-19 prognosis, in terms higher risk of hospitalizations, intensive care unit admissions, or death that is related to COVID-19. All of these studies have detected an association between $PM_{2.5}$ and the risk of severe COVID-19 outcomes, including hospitalizations (Bowe et al. 2021; Chen et al. 2022; Mendy et al. 2021), intensive care unit visits (Bozack et al. 2022; Chen et al. 2022), or death (Bozack et al. 2022; Chen et al. 2022).

The internationally unique infrastructure of the Danish population and health registries, has access to highly precise historical residential address histories, estimates of air pollution for more than 40 years, COVID-19 deaths and hospitalization data, as well as SES and comorbidity data at the individual level for the entire Danish population. This infrastructure provides a framework that can directly address the limitations of the ecological approach and those from other individual-level studies, particularly selection of subjects who have access to polymerase chain reaction (PCR) testing, with sufficient control for confounding, and collinearity between population density and exposure. This research was designed to provide new, high quality data to support the rapidly emerging evidence base on the potential association between long-term exposure to air pollution and susceptibility to COVID-19. The evaluation of this evidence will be crucial for the scientific and public health community and policymakers in their work in mitigating risk and developing solutions during the global COVID-19 crisis.

SPECIFIC AIMS

Here we aim to investigate whether long-term exposure to air pollution is associated with increased risk of mortality and morbidity related to COVID-19 and to identify the most susceptible groups by age, sex, SES, ethnicity, and comorbidities. Specific aims:

1. Examine whether long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 are associated with the risk of contracting COVID-19, in terms of COVID-19 incidence, hospitalizations, or death in the general population.
2. Identify subgroups that are susceptible to air pollution–related COVID-19 morbidity and mortality by age, sex, SES (education, individual income, household income, wealth, occupational status, civil status, housing tenure, and household size, type, and composition), ethnicity (Danish as well as non-Western and Western origin), and comorbidity (cardiovascular disease, respiratory disease, acute lower respiratory infections, lung cancer, diabetes, and dementia).
3. Examine whether long-term exposure to $PM_{2.5}$, PM_{10}, NO_2, BC, 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.

METHODS AND STUDY DESIGN

STUDY POPULATION

We created a population-based nationwide cohort called the "Long-term exposure to AIR pollution and COVID-19 mortality and morbidity in DENmark" (AIRCODEN) by including all Danish residents who were 30 years or older on March 1, 2020 and had lived in Denmark for at least 1 year prior to this date.

COVID-19 OUTCOME DEFINITIONS

Danish Statens Serum Institut, under the Danish Ministry of Health, is responsible for the Danish preparedness against infectious diseases and is in charge of surveillance of the COVID-19 pandemic in Denmark. The surveillance of the COVID-19 infections is based on the results of the tests from microbiological departments at the Danish hospitals and testing centers, and from Statens Serum Institut's own laboratory, which are collected centrally in the Danish Microbiological Database (*https://miba.ssi.dk/service/english*). Data include results from PCR tests for the COVID-19 virus. We obtained data on COVID-19 from the Danish Health Data Authority, notably with a 5-month delay due to COVID-19 lockdown measures, which slowed down processing of the data for research.

The COVID-19 data available for researchers at the Danish Health Authority include information on COVID-19 test date, test result, hospital admission date, place of death, death date, international travel prior to admission/death, and country of travel. A detailed description of the available data is provided in Table A1 in Appendix A (available on HEI website). The Statens Serum Institut and Danish Health Ministry note that researchers should be aware of two important facts regarding the use of Danish COVID-19 data in research: (1) that COVID-19 surveillance data are dynamic in that the Statens Serum Institut worked continuously to improve their surveillance algorithms, which may have resulted in changes to their algorithms during the time of this study (there were no major changes in algorithm relevant for the analyses of COVID-19 incidence, hospitalization, or death data in this project), and (2) that changes in test strategy affect the population in that COVID-19 data are affected by a continuous change in the testing strategy, which implies that the population of those with confirmed COVID-19 infections cannot be compared over time.

Using unique personal identification numbers, we linked the AIRCODEN cohort participants with the Danish National COVID-19 Surveillance System database. PCR testing in Denmark was offered to all citizens, free of charge and easily accessible, thus providing a unique opportunity to trace COVID-19 infection in all Danish residents — though, notably with very poor testing capacity in the first wave and much larger testing capacity in the second pandemic wave starting on August 1, 2020 (**Figure 1**). We defined COVID-19 outcomes as incidence (first positive PCR test for SARS-CoV-2), hospitalization (hospital admission for more than 12 hours within 14 days after the first positive PCR test for SARS-CoV-2), and death (death within 30 days of the detection of SARS-CoV-2 infection). Note that the statistics on COVID-19 fatalities include deaths recorded within 30 days of the detection of COVID-19 infection in the individual, but that COVID-19 is not necessarily the underlying cause of death. We also defined death from any cause as an additional outcome, in order to compare the size of association between air pollution and COVID-19 with that for all-cause mortality, recently reported in the nationwide Danish cohort from year 2000.

In this report, we refer to SARS-CoV-2 as the virus and to COVID-19 as the disease manifestation in those who contracted SARS-CoV-2. In this project we were mainly interested in air pollution association with the risk of COVID-19 (i.e., the disease resulting from infection of SARS-CoV-2), keeping in mind that it is possible to have asymptomatic SARS-CoV-2 infection (i.e., infection without diseases, symptoms, etc.). Thus, we defined three possible definitions of the COVID-19: incidence (positive test for SARS-CoV-2, since we do not have data to separate asymptomatic SARS-CoV-2 cases and those who developed diseases COVID-19), hospitalization, and mortality.

COVARIATE AND COMORBIDITY DEFINITIONS

We have extracted individual-level SES information for year 2019 from the Danish national registers with information

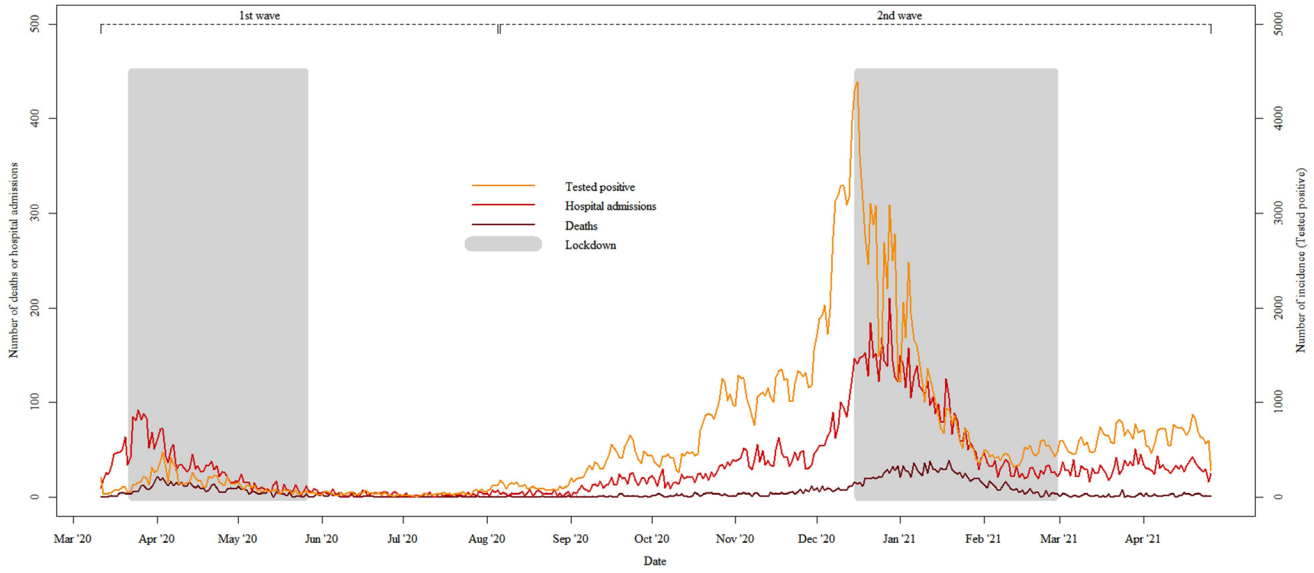

Figure 1. The COVID-19 pandemic in Denmark between March 1, 2020, and April 26, 2021. Daily numbers of COVID-19 positive cases, hospital admissions, and deaths in Denmark.

on individual SES for all Danish citizens, including occupation, personal income and transfer of welfare payments (Baadsgaard and Quitzau 2011), personal labor market affiliation (Petersson et al. 2011), and education (Jensen and Rasmussen 2011), as well as civil status, household composition, and country of origin available from the Danish Civil Registration System (Schmidt et al. 2014). The following individual-level variables were defined based on the register data from 2019:

- Marital status (married/registered partnership; divorced; widow/widower; single)
- Highest completed education (primary/basic education; vocational training; short higher education; medium higher education; long higher education — college or higher)
- Occupational status (primary, upper secondary, vocation/qualifying, vocation bachelor/short higher education, college level or higher)
- Individual wealth, in tertiles (the approximate difference between all assets and liabilities in DKK/year)
- Family/household disposable income, in tertiles (DKK/year)
- Household size (one, two, three, four, five or more persons living in household)

The following area-level/neighborhood variables were defined at parish level defined from the register data for year 2019:

- Population density (number of people/km^2)
- Mean income (DKK/year)
- Median wealth (DKK/year)
- Percent unemployment
- Percent primary or lower education
- Corresponding SES (including mean income, median wealth, percent unemployment, and percent primary or lower education) difference between municipality and parish
- Municipality-level access to healthcare (number of general practitioners/citizens)
- Lung cancer incidence rate (proxy for parish smoking rates)
- Diabetes incidence rate (proxy for parish obesity rates)

In Denmark there are 5 regions, 98 municipalities, and 2,158 parishes. The five regions are the Capital Region (29 municipalities), Southern Denmark Region (22 municipalities), Central Denmark Region (19 municipalities), Zealand Region (17 municipalities), and North Denmark (11 municipalities). In Denmark, a parish is a local ecclesiastical unit in the Church of Denmark. Each parish is assigned to a physical church, and the church's administration handles the area's civic registration of births, marriages, and deaths. Each Danish municipality is composed of one or more parishes.

Ethnicity was defined by country of origin (Denmark; Western countries [all 28 European Union countries and Andorra,

Iceland, Liechtenstein, Monaco, Norway, San Marino, Switzerland, Vatican State, Canada, the United States, Australia, and New Zealand]; and non-Western [all others]).

Comorbidities (i.e., the prevalence of a specific disease) were defined as a record of hospital contact (inpatient, outpatient, or emergency) in the Danish National Patient Register (Schmidt et al. 2015) for that specified disease prior to AIRCODEN baseline on March 1, 2020, as defined in **Table 1**. Note that we had data from the Danish National Patient Register available from the onset of the register in 1979 until December 31, 2018.

AIR POLLUTION EXPOSURE

We used the Danish integrated Danish Eulerian Hemispheric Model (DEHM)/Urban Background Model (UBM) estimates of annual means of NO_2, $PM_{2.5}$, PM_{10}, BC, and O_3 at a 1×1 km resolution from 1979–2019, assigned to residential addresses of AIRCODEN cohort participants. The DEHM is a chemistry-transport model (Brandt et al. 2012), and the UBM (Brandt et al. 2003) includes several domains with different spatial resolutions to calculate intercontinental and regional transport of air pollution, while achieving a high resolution over Denmark. The models were validated against measurements and showed good performance (Hvidtfeldt et al. 2018; Khan et al. 2019). The main exposure proxy used was a 1-year mean exposure at residence in 2019, as seen on Figure 2, and additional analyses was performed with 3-year (2017–2019) and 10-year mean exposure. We defined these three exposure windows to examine whether more recent exposure to air pollution (in 2019, a year before pandemic) or the accumulation of exposure over a long period of time for up to ten years, were the most relevant for the risk of contracting SARS-CoV-2.

Traffic-related pollutants NO_2 and BC are highest in Denmark in the urban areas, whereas O_3 is highest at the rural and coastal areas (Figure 2). Apart from high levels of $PM_{2.5}$ in urban areas, levels are also high in Southeastern Denmark due to significant contribution of long-range transported secondary particles from Central and Eastern Europe.

We also used the European-wide hybrid land use regression (LUR) model, developed within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project (*http://www.elapseproject.eu/*), which provides annual mean concentrations of $PM_{2.5}$, NO_2, BC, and O_3 for the year 2010 at a 100×100-m resolution, (de Hoogh et al. 2016) and which has been used in other studies on air pollution and all-cause mortality in Europe and Denmark. In brief, the LUR model utilized routine monitoring data from the European Environment Agency AirBase for $PM_{2.5}$ and NO_2, and European Study of Air Pollution Effects (ESCAPE) monitoring data for BC as the dependent variable. Satellite data, dispersion model estimates, land use, and traffic variables were predictors to estimate annual mean pollutant concentrations. The models performed well in five-fold hold-out validation, explaining 72%, 59%, and 54% of spatial variability of the measured concentrations for $PM_{2.5}$, NO_2, and BC, respectively (de Hoogh et al. 2018). We used the ELAPSE model in addition to the Danish model to test whether our results were robust to different methods of estimating long-term exposure to air pollution.

STATISTICAL METHODS AND DATA ANALYSIS

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19 INCIDENCE, HOSPITALIZATION, AND MORTALITY

We used stratified Cox proportional hazard models with calendar time in days as the underlying timescale to examine the associations of air pollutants (single-pollutant models) with COVID-19 incidence, hospitalization, death, or all-cause mortality, with censoring at the date of death from other reasons, emigration, or the end of follow-up on April 26, 2021, whichever came first. We fitted three models with increasing control for the individual- and area-level covariates: Model 1, which adjusted for the calendar time (time axis), age (strata by 5-year age band), sex (strata), and region of residence (strata) (region was not included in all-cause mortality analyses); Model 2, which additionally adjusted for individual-level SES, including marital status (unmarried, divorced, widowed, married/registered partnership), highest completed education (primary, upper secondary, vocation/qualifying, vocation bachelor/short higher education, college level or higher), occupational status (unemployed, employed, or sick/welfare support/student/pension/others), individual wealth (tertile), family income (tertile), and household size (one, two, three, four, five, and above persons living in household); and Model 3 (main model), which additionally adjusted for population-level SES including parish-level population density, municipality-level access to healthcare, parish-level SES factors (mean income, median wealth, percentage of unemployment, percentage of primary or low education, and the SES difference between municipality and parish). We have extensively adjusted for SES both at individual- and area-level because air pollution exposure and risk of COVID-19 are both related to SES. The Cox model is a standard model used to examine the association between air pollution and health outcomes, which are assessed prospectively in time-to-event format. To account for the spatial correlation of observations within the same parish, we used the Huber sandwich estimator for all models to robust the variance estimation.

We fitted single-pollutant models for annual mean exposure in 2019 (main analyses) and for three-year (2017–2019) and ten-year (2010–2019) means of $PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 estimated by the Danish DEHM/UBM model, as well as for 2010 annual mean of $PM_{2.5}$, NO_2, BC, and O_3 estimated by ELAPSE model. These different approaches were used to examine which exposure window to air pollution may be most relevant for the immune response relevant for infection by SARS-CoV-2: is it more recent exposures, captured best by the annual mean exposure in 2019, or accumulated exposure over

Table 1. Definition and Prevalence of Comorbidities Among the 3,721,813 Participants of the AIRCODEN Cohort at the Study Baseline on March 1, 2020[a]

	ICD-10 Codes	ICD-8 Codes	**Prevalence, *N* (%)**
Cardiovascular disease	**I00–99**	**400–459**	**934,898 (25.1%)**
Myocardial infarction	I21	410	91,070 (2.4%)
Heart failure	I50	427	51,623 (1.4%)
Atrial fibrillation	I48	427.4, 427.9	128,031 (3.4%)
Stroke (ischemic included)	I61–64	431, 432, 433, 434, 436	103,715 (2.8%)
Respiratory disease	**J00–J99**	**460–519**	**880,018 (23.6%)**
Asthma	J45–46	493	127,744 (3.4%)
COPD	J40–44	490–492	79,674 (2.1%)
Acute lower respiratory infection	J12–18, J20–22	480–486, 466	245,782 (6.6%)
Pneumonia	J12–18	480–486	217,015 (5.8%)
Influenza	J09–11	487–488	21,135 (0.6%)
Lung cancer	**C34**	**162.2–162.9**	**10,425 (0.3%)**
Diabetes	**E10–14, H36, O24 (excluded O24.4)**	**249, 250**	**121,671 (3.3%)**
Dementia	**F00–03, G30, G31.8–9**	**290.09–11,290.19; 293.09–11,293.19**	**16,467 (0.4%)**

COPD = chronic obstructive pulmonary disease.

[a] ICD-8/10: International Classification of Diseases 8th/10th version. ICD-8 was used before and ICD-10 after January 1, 1994 (ICD-9 was never implemented in Denmark).

longer time, captured by three- or ten-year mean exposure? We also conducted these analyses to test robustness of our results to different modeling approaches used for estimating exposures to air pollution.

To evaluate the shape of the associations for each pollutant and examine whether there is a threshold below which air pollution does not pose a risk for COVID-19, we have estimated exposure–response functions by applying natural cubic splines with three degrees of freedom. To examine whether the associations with air pollution may have changed over time during the study period due to differences in testing capacity, stringency of lockdown measures, compliance with lockdown and other (wearing masks, physical distancing, compulsory testing, etc.) pandemic measures, as well as COVID-19 strains, we estimated associations separately in two pandemic waves: March 1–July 31, 2020, and August 1, 2020–April 26, 2021.

We have aimed to identify groups of Danish residents who were most susceptible and most likely to contract SARS-CoV-2 virus and develop COVID-19 due to air pollution, by demographics, SES, and comorbidities. Specifically, effect modification of an association of $PM_{2.5}$ and NO_2 with COVID-19 incidence, hospitalization, and mortality by sex, age, individual-level SES, ethnicity and comorbidities with cardiovascular disease, respiratory disease, acute lower respiratory infections, diabetes, lung cancer, dementia, and diabetes, were evaluated by entering an interaction term (one at the time) into the model and tested by the Wald test at multiplicative scale. We fitted mutually adjusted two-pollutant models for pollutant combinations for which the Pearson correlation coefficient is less than 0.7.

We performed several sensitivity analyses. To evaluate possible confounding by missing information on smoking and body mass index (BMI), which are not readily available for the Danish population, we have additionally adjusted for parish-level chronic obstructive pulmonary diseases or lung cancer prevalence rates (proxies for smoking) and parish-level diabetes prevalence rates (proxy for obesity). We have also applied the indirection adjustment (Shin et al. 2014) using the associations between air pollution and smoking and BMI based on the Danish National Survey 2017, which included data on 183,372 Danes who were 18 years and older. This survey is considered to have the most representative data on Danish adult populations' lifestyle factors. To make the indirect adjustment, we have linked the Danish National Survey participants to the air pollution estimates (the Danish integrated DEHM/UBM model) at their residence in 2017, and then estimated the association between lifestyle factors (e.g.,

smoking, BMI, and physical activity) and different air pollutants. These effect estimates were used to correct the effect estimates of the association between the specific air pollutant and COVID-19 incidence, mortality, and hospitalization. We have additionally performed sensitivity analyses of association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality using Poisson regression instead of Cox regression, and estimated rate ratio (RR).

The weakness of our approach is that not all Danish residents have been tested for COVID-19, and that those who chose to get tested may be somehow different from those who did not, and that results of this study are not generalizable to the latter. Thus, to explore whether associations are affected by a possible selection bias in who gets tested, we have estimated associations in a subsample of population who were tested for COVID-19. Another issue with COVID-19 is that there were fast-changing strategies in testing, such as population adaptation, and lockdown-measures, which all may have had an impact on the effect of air pollution on COVID-19. To examine whether changes in testing capacity and prevention measures over time and space, in different parts of the country, affected associations of air pollution with COVID-19, we used time-varying Cox models with adjusting for covariates in Model 3 and monthly municipality-level SARS-CoV-2–positive rate based on PCR tests. By estimating SARS-CoV-2–positive rate every month in every municipality, we could account for the development of the COVID-19 pandemic over space and time in Denmark, and account for it in our analyses (Danesh Yazdi et al. 2021, Lin and Ying 1994).

Only subjects with complete information for Model 3 variables were included in the analyses. We presented HRs and 95% CIs per interquartile range (IQR) increase in pollutant. We conducted analyses using R statistical software (version 4.1.2).

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19 HOSPITALIZATION AND MORTALITY AMONG COVID-19 CASES

In this part of the analyses we examined whether in those who contracted SARS-CoV-2, air pollution increased the risk of the development of more severe COVID-19, requiring hospitalization or resulting in death. We used a logistic regression model to examine the associations of air pollutants with COVID-19 hospitalization and death among 138,742 individuals who tested positive for COVID-19. We fitted three models with increasing control for the individual- and area-level covariates: Model 1 adjusted for calendar time (natural spline with eight degrees of freedom), sex, and age at baseline (5-year bands); Model 2 additionally adjusted for civil status, household size, individual wealth, family income, education, and occupational status; and Model 3 further adjusted for parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the difference of those variables between parish and municipality, and municipality-level access to healthcare. We fitted single-pollutant models for annual mean exposure in 2019 (main analyses), and for a 3-year (2017–2019) mean of $PM_{2.5}$, PM_{10}, NO_2, BC, and O_3 estimated by the Danish DEHM/UBM model. The study was approved by the Danish Data Protection Agency.

RESULTS

Of the 3,743,013 AIRCODEN participants who were 30 years or older and resided in Denmark on March 1, 2020, (and at least 1 year prior), we excluded 8,397 subjects with missing data on air pollution exposure due to missing or incomplete geocoding of residential address, 676 with missing data on individual SES information, and 12,127 subjects with missing parish-level SES information due to missing or incomplete linkage between individual address and its parish. In addition, three individuals were excluded from incidence and hospitalization analyses due to record of SARS-CoV-2 positive test before March 1, 2020, leaving 3,721,813 subjects for final analyses.

During 14 months follow-up (411–417 days) covering two pandemic waves (**Figure 1**), 138,742 individuals tested positive for SARS-CoV-2, 11,270 were hospitalized, and 2,557 died from COVID-19. Compared with the total population, subjects who died or were hospitalized from COVID-19, or those who died from any cause, were less likely to be women, highly educated, employed, married or live with a partner, or have high income (**Table 2**). However, reverse patterns with less pronounced differences, were observed with incident COVID-19 cases. The vast majority (92% or 128,262 cases) of incident COVID-19 cases (or SARS-CoV-2 positive tests) were observed in the second pandemic wave, whereas only 8% or 10,480 cases were observed during first wave. Correspondingly, 8,908 or 79% of hospitalization, 1,921 or 75% of COVID-19 deaths, and 40,331 or 65% of deaths from any causes were registered in the second wave.

Mean levels of $PM_{2.5}$, NO_2, and BC in 2019 were 7.43, 10.7, and 0.33 μg/m^3, respectively, and were slightly higher in COVID-19 cases than in the total population (Table 2). The strongest positive correlation was observed between NO_2 and BC (0.75) and NO_2 and $PM_{2.5}$ (0.61), and negative between NO_2 and O_3 (–0.86), and BC and O_3 (–0.68) (**Figure 3**). PM_{10} was poorly correlated with all other pollutants.

We detected strong, significantly positive associations of 2019 annual exposure to $PM_{2.5}$, NO_2, and BC with all three COVID-19 outcomes (incidence, hospitalization, and mortality) (**Table 3**), mostly strongest for mortality. The corresponding HRs and 95% CI from Model 3 were 1.23 (CI: 1.04–1.44) per 0.55-μg/m^3 increase in $PM_{2.5}$, 1.18 (CI: 1.03–1.34) per 3.49-μg/m^3 increase in NO_2, 1.06 (CI: 1.02–1.10) per 0.09-μg/m^3 increase in BC, and 1.19 (CI: 1.07–1.33) per 1.14-μg/m^3 increase in PM_{10}. Somewhat weaker (almost half of those observed with mortality), but still positive and statistically significant associations were found for $PM_{2.5}$ and

Table 2. Characteristics Among the 3,721,813 Participants of the AIRCODEN Cohort at the Study Baseline on March 1, 2020

	Total Population	COVID-19 Incidence	COVID-19 Hospitalization	COVID-19 Mortality	All-Cause Mortality
N	3,721,813	138,742	11,270	2,557	62,359
Person-day at risk	–	1,531,385,032	1,549,500,678	1,551,066,930	1,551,066,930
Follow-up time, day	–	411	416	417	417
Individual level					
Age, year (mean ± SD)	56.3 ± 15.6	52.0 ± 14.6	68.1 ± 15.6	81.1 ± 10.3	78.6 ± 12.2
Age > 65 years old, *N* (%)	1,157,323 (31.1%)	25,207 (18.2%)	6,859 (60.9%)	2,383 (93.2%)	53,873 (86.4%)
Female, *N* (%)	1,904,171 (51.2%)	72,250 (52.1%)	5,024 (44.6%)	1,162 (45.4%)	30,520 (48.9%)
Employed, *N* (%)	2,124,059 (57.1%)	96,036 (69.2%)	3,042 (27.0%)	119 (4.6%)	4,247 (6.81%)
Married/Partner, *N* (%)	2,069,552 (55.6%)	84,220 (60.7%)	6,019 (53.4%)	991 (38.8%)	23,548 (37.8%)
Income					
Low, *N* (%)	1,082,427 (29.1%)	38,286 (27.6%)	5,266 (46.7%)	1,454 (56.9%)	36,205 (58.1%)
Middle, *N* (%)	1,245,348 (33.5%)	45,530 (32.8%)	3,408 (30.2%)	815 (31.9%)	18,717 (30.0%)
High, *N* (%)	1,394,038 (37.5%)	54,926 (39.6%)	2,596 (23.0%)	288 (11.3%)	7,437 (11.9%)
Danish origin, *N* (%)	3,263,925 (87.7%)	103,383 (74.5%)	8,739 (77.5%)	2,316 (90.6%)	59,186 (94.9%)
Higher education, *N* (%)	477,065 (12.8%)	19,288 (13.9%)	742 (6.6%)	99 (3.9%)	2,436 (3.9%)
Wealth					
Low, *N* (%)	1,072,333 (28.8%)	47,463 (34.2%)	2,175 (19.3%)	202 (7.9%)	6,307 (10.1%)
Middle, *N* (%)	1,122,312 (30.2%)	44,976 (32.4%)	4,670 (41.4%)	1,255 (49.1%)	27,735 (44.5%)
High, *N* (%)	1,527,168 (41.0%)	46,303 (33.4%)	4,425 (39.3%)	1,100 (43.0%)	28,317 (45.4%)
Family size ≤ 2, *N* (%)	3,313,067 (89.0%)	117,557 (84.7%)	9,856 (87.5%)	2,399 (93.8%)	58,909 (94.5%)
Area level[a]					
Mean income, (mean ± SD)	287,915 ± 67,593	289,951 ± 74,259	287,678 ± 75,397	291,937 ± 74,262	281,695 ± 64,536
Median wealth (mean ± SD)	120,780 ± 169,063	110,713 ± 176,085	108,098 ± 176,085	115,528 ± 180,480	114,052 ± 158,615
Unemployment rate (mean ± SD)	1.0% ± 0.5%	1.2% ± 0.5%	1.2% ± 0.5%	1.1% ± 0.5%	1.0% ± 0.5%
Low education rate (mean ± SD)	22.6% ± 7.6%	21.5% ± 7.6%	22.3% ± 7.7%	21.7% ± 7.6%	23.9% ± 7.5%
Population density, *N*/km^2 (mean ± SD)	20.8 ± 42.3	30.2 ± 51.4	27.8 ± 45.8	28.2 ± 44.6	17.1 ± 33.5
GP visit rate (mean ± SD)	77.3% ± 2.0%	76.8% ± 2.2%	76.9% ± 2.1%	76.9% ± 2.0%	77.5% ± 1.8%
Air pollution in 2019 based on DEHM/UBM Model					
$PM_{2.5}$ (mean ± SD)	7.4 ± 0.5	7.5 ± 0.4	7.5 ± 0.4	7.5 ± 0.4	7.4 ± 0.5
NO_2 (mean ± SD)	10.7 ± 2.4	11.5 ± 2.4	11.4 ± 2.3	11.5 ± 2.3	10.6 ± 2.3
BC (mean ± SD)	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
PM_{10} (mean ± SD)	12.7 ± 0.9	12.6 ± 0.8	12.5 ± 0.8	12.5 ± 0.7	12.8 ± 0.9
O_3 (mean ± SD)	54.5 ± 2.2	54.0 ± 2.0	54.1 ± 2.0	54.1 ± 1.9	54.7 ± 2.2

GP = general practitioner; DEHM/UBM = Danish Eulerian Hemispheric Model/Urban Background Model.

[a] Area level variables were based on the parish, the smallest administrative unit in Denmark.

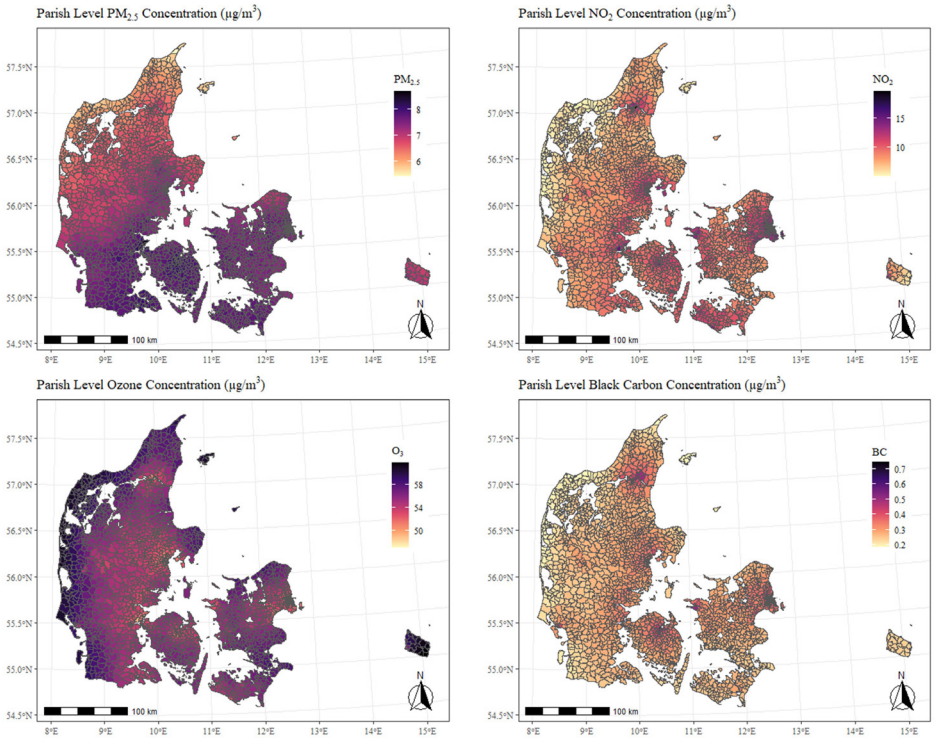

Figure 2. Annual mean parish levels of $PM_{2.5}$, NO_2, BC, and O_3 in 2019 in Denmark. BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; $PM_{2.5}$ = particulate matter with diameter ≤2.5 μm.

PM_{10} and COVID-19 incidence and hospitalizations, whereas associations with NO_2 and BC were almost identical for all three outcomes. We found significant inverse associations of O_3 with all three COVID-19 outcomes and no association of either PM_{10} or O_3 with all-cause mortality. Associations with COVID-19 outcomes observed in the crude model, adjusted for age, sex, and region (Model 1), remained largely unchanged when adjusting for individual-level SES (Model 2), but attenuated substantially when adjusting for area-level SES (Model 3). For all-cause mortality, estimates remained almost identical in all three models. Compared with 1-year mean, associations with COVID-19 were almost identical with 3-year (slightly stronger) and 10-year (slightly weaker) exposure windows (**Figure 4**).

Air pollution estimated by the European ELAPSE model for year 2010 was higher than air pollution estimated by the Danish DHEM/UBM model for year 2019 (**Table 4**), explained by differences in the two modeling approaches as well as reduction in air pollution since 2010. Air pollutants estimated by the ELAPSE model showed moderate-to-good correlation with the Danish DEHM/UBM model, with correlation of 0.51 between $PM_{2.5}$ from two models, 0.63 for NO_2, and 0.47 for both, BC and O_3 (**Figure 5**). Analyses with ELAPSE model air pollutants showed strong and significantly positive associations with all COVID-19 outcomes as well as with all-cause mortality, comparable to those observed with the Danish DEHM/UBM model (**Figure 6**), although somewhat weaker for $PM_{2.5}$, NO_2, and O_3, and stronger for BC.

Exposure–response functions were linear or curvilinear for the majority of the pollutants and COVID-19 outcomes (**Figure 7**), in line with finding of generally stronger associations at lower exposure ranges, well below current EU limit values of 25 μg/m³ for $PM_{2.5}$ and 40 μg/m³ for NO_2 (Appendix Table A2; available on the HEI website).

We found no associations in the first pandemic wave, but significant and positive associations of $PM_{2.5}$, NO_2, and BC in the second pandemic wave for all three COVID-19 outcomes (**Figure 8**). PM_{10} showed stronger associations in the first pandemic wave. In the two-pollutant models, associations with NO_2 and BC were robust to adjustment for $PM_{2.5}$, whereas those with $PM_{2.5}$ attenuated to null with COVID-19 incidence and hospitalization and attenuated by a half for mortality (Appendix Table A3). Associations remained unchanged with three approaches for adjusting for missing information on smoking and BMI (Appendix Figure A1) when limiting population to those who were tested (Appendix Figure A2) and when adjusting for spatiotemporal development

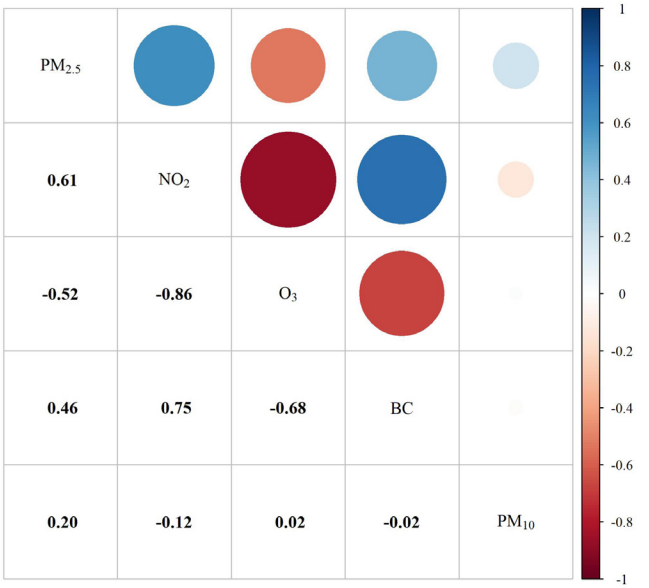

Figure 3. Pearson correlation coefficients between annual mean air pollution levels at residence in 2019 among the 3,721,813 participants of the AIRCODEN cohort. BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 μm, respectively).

Table 3. The Association Between Long-Term Exposure to Air Pollution and COVID-19 Incidence, Hospitalization, and Mortality, as well as All-Cause Mortality Among the 3,721,813 Participants of the AIRCODEN Cohort[a,b]

	Model 1[b] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[b] HR (95% CI)
COVID-19 Incidence[c] (*N* = 138,742)			
$PM_{2.5}$	**1.16 (1.12–1.21)**	**1.23 (1.18–1.27)**	**1.10 (1.05–1.14)**
NO_2	**1.25 (1.20–1.30)**	**1.32 (1.27–1.37)**	**1.18 (1.14–1.23)**
BC	**1.07 (1.03–1.10)**	**1.07 (1.04–1.11)**	**1.05 (1.01–1.08)**
O_3	**0.82 (0.80–0.85)**	**0.79 (0.77–0.81)**	**0.86 (0.84–0.89)**
PM_{10}	**1.05 (1.01–1.08)**	**1.07 (1.04–1.11)**	**1.09 (1.06–1.12)**
COVID-19 Hospitalization[c] (*N* = 11,270)			
$PM_{2.5}$	**1.22 (1.15–1.30)**	**1.24 (1.17–1.32)**	**1.09 (1.01–1.17)**
NO_2	**1.35 (1.27–1.44)**	**1.35 (1.28–1.43)**	**1.19 (1.12–1.27)**
BC	**1.08 (1.04–1.12)**	**1.08 (1.04–1.12)**	**1.05 (1.01–1.08)**
O_3	**0.77 (0.74–0.81)**	**0.77 (0.74–0.81)**	**0.86 (0.82–0.91)**
PM_{10}	**1.10 (1.03–1.17)**	**1.10 (1.04–1.17)**	**1.14 (1.07–1.20)**
COVID-19 Mortality (*N* = 2,557)			
$PM_{2.5}$	**1.33 (1.17–1.50)**	**1.31 (1.16–1.48)**	**1.23 (1.04–1.44)**
NO_2	**1.34 (1.21–1.49)**	**1.29 (1.16–1.42)**	**1.18 (1.03–1.34)**
BC	**1.09 (1.05–1.14)**	**1.09 (1.05–1.13)**	**1.06 (1.02–1.10)**
O_3	**0.78 (0.72–0.84)**	**0.80 (0.74–0.87)**	**0.87 (0.78–0.96)**
PM_{10}	**1.15 (1.04–1.27)**	**1.13 (1.02–1.25)**	**1.19 (1.07–1.33)**
All-Cause Mortality (*N* = 62,359)			
PM_{25}	**1.02 (1.00–1.03)**	**1.02 (1.01–1.03)**	**1.02 (1.01–1.03)**
NO_2	**1.05 (1.02–1.08)**	**1.04 (1.02–1.06)**	**1.04 (1.01–1.07)**
BC	**1.02 (1.01–1.04)**	**1.02 (1.01–1.03)**	**1.01 (1.00–1.02)**
O_3	0.98 (0.96–1.00)	0.99 (0.97–1.00)	1.00 (0.98–1.02)
PM_{10}	**0.99 (0.97–1.00)**	**0.96 (0.95–0.98)**	**0.98 (0.96–0.99)**

HR = hazard ratio; CI = confidence interval; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 μm, respectively.

[a] Results are presented for interquartile range increase: 0.55 μg/m³ for $PM_{2.5}$, 3.49 μg/m³ for NO_2, 0.09 μg/m³ for BC, 2.79 μg/m³ for O_3, and 1.14 μg/m³ for PM_{10}. Boldfaced text indicates statistically significant values with $P < 0.05$.

[b] Model 1 adjusted for calendar time (time axis), sex (strata), age at baseline (strata), and region (strata); Model 2 additionally adjusted for civil status, household size, individual wealth, family income, education, and occupational status; Model 3 further adjusted for parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the difference of those variables between parish and municipality, and municipality-level access to healthcare (analysis for all-cause mortality was not stratified by regions).

[c] *N* = 3,721,810 (three people excluded due to COVID-19 infection before baseline on March 1, 2020).

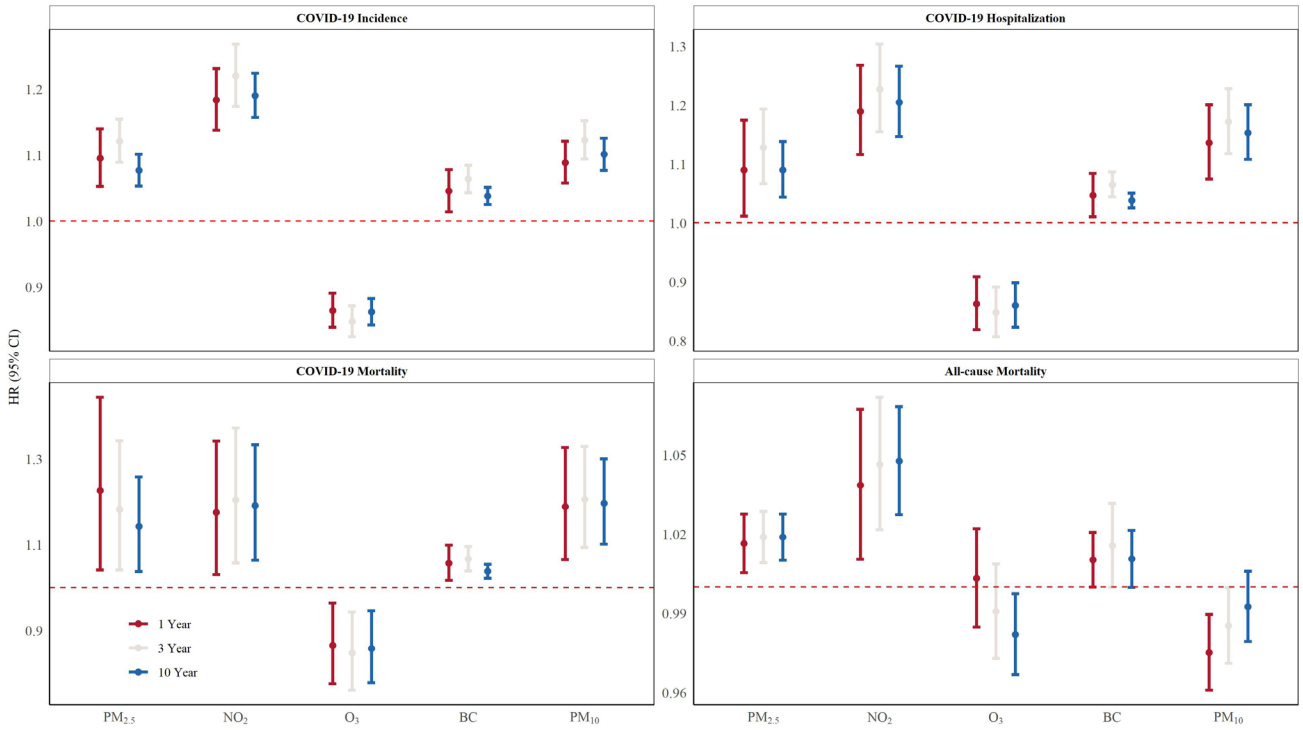

Figure 4. The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality, among the 3,721,813 participants of the AIRCODEN cohort using three exposure windows [1-year mean (2019), 3-year mean (2017–2019), and 10-year mean (2010–2019)]. HR = hazard ratio; CI = confidence interval; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 µm, respectively. Results are presented for interquartile range increase: 0.55 µg/m³ for $PM_{2.5}$, 3.49 µg/m³ for NO_2, 0.09 µg/m³ for BC, 2.79 µg/m³ for O_3, and 1.14 µg/m³ for PM_{10}. Model adjusted for calendar time (time axis), sex (strata), age at baseline (strata), and region (strata); individual covariates (civil status, household size, individual wealth, family income, education, and occupational status); and area-level covariates (parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the differences of socioeconomic variables between parish and municipality, and municipality-level access to healthcare). Analysis for all-cause mortality was not stratified by regions.

Figure 5. Pearson correlation coefficients between air pollutants estimated by DEHM/UBM^D model in 2019 and the ELAPSE^E model in 2010 among the 2,205,957 participants of the AIRCODEN cohort who had data on both exposures. BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; and PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 µm, respectively.

Table 4. Summary of the Air Pollution Level Estimated by DEHM/UBM Model in 2019 and the ELAPSE Model in 2010 Among the Subset of 2,205,957 Participants of the AIRCODEN Cohort Who Had Data on Both Exposures

Air Pollution	DEHM/UBM Model Mean ± SD	IQR	ELAPSE Model Mean ± SD	IQR
$PM_{2.5}$	7.4 ± 0.5	0.6	12.3 ± 1.5	2.0
NO_2	10.5 ± 2.3	3.3	19.9 ± 7.9	10.1
O_3	54.7 ± 2.2	2.9	80.4 ± 4.3	4.1
BC	0.3 ± 0.1	0.1	1.0 ± 0.4	0.5

BC = black carbon; NO_2 = nitrogen dioxide; O_3 =ozone; $PM_{2.5}$ = particulate matter with diameter ≤2.5 μm; SD = standard deviation; IQR = interquartile range; DEHM/UBM = Danish Eulerian Hemispheric Model/Urban Background Model; ELAPSE Model = Effects of Low-Level Air Pollution: A Study in Europe.

of the epidemic via municipality-level SARS-CoV-2 positivity rates (Appendix Table A4). Similarly, our observed associations were almost identical when using Poisson regression instead of Cox regression models (Appendix Table A5).

We found strongest associations of NO_2 with COVID-19 incidence in the those aged 65 years old or older, and of both $PM_{2.5}$ and NO_2 in those with lowest education, income, and wealth, those who were unemployed, or living in large households with five inhabitants or more (**Figure 9**). We also found strongest associations in those who were born in Denmark and those from non-Western countries, whereas no association was detected in those originating from Western countries. We found no difference in associations between men and women. When considering comorbidities at the study baseline, we found the strongest associations with both $PM_{2.5}$ and NO_2 in those with prior cardiovascular disease, which was most pronounced for myocardial infarction and stroke, but also apparent for heart failure and atrial fibrillation (**Figure 10**). We also detected stronger associations in those with prior respiratory disease, although less pronounced in those

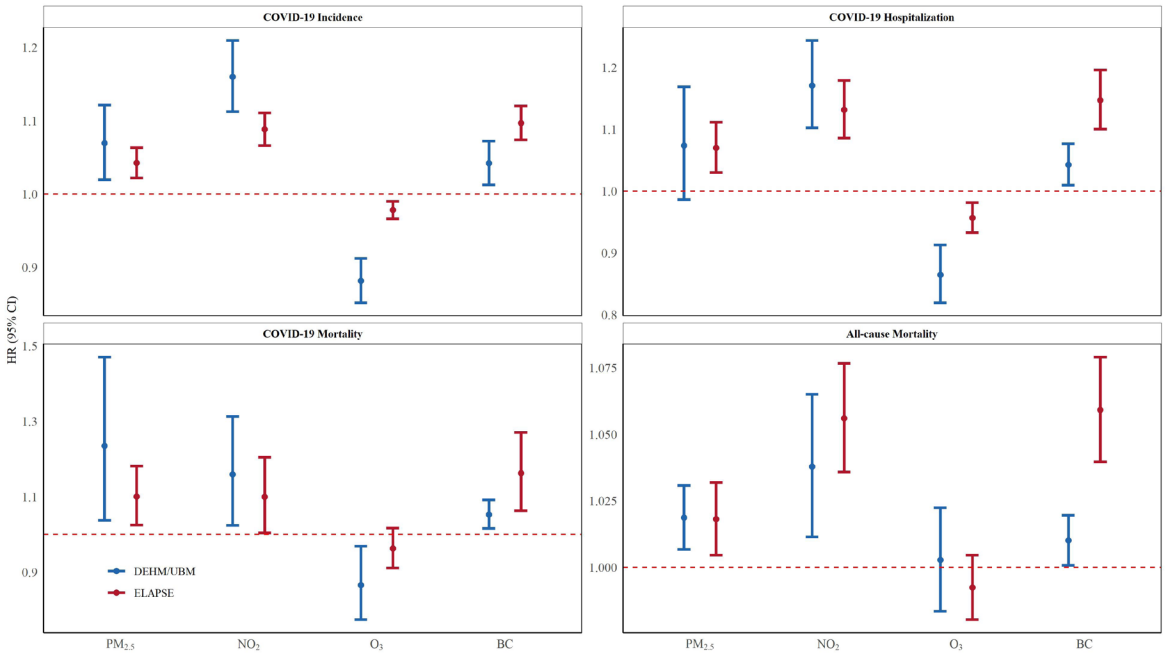

Figure 6. The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 2,205,957 participants of the AIRCODEN cohort, using DEHM/UBM model (blue) in 2019 and the ELAPSE model (red) in 2010. HR = hazard ratio; CI = confidence interval; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; and PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 μm, respectively. Results are presented for model-specific interquartile range (IQR) increase. For DEHM/UBM model IQRs are: 0.6 μg/m³ for $PM_{2.5}$, 3.3 μg/m³ for NO_2, 0.1 μg/m³ for BC, 2.9 μg/m³ for O_3; and for ELAPSE IQRs are: 2.0 μg/m³ for $PM_{2.5}$, 10.1 μg/m³ for NO_2, 0.5 μg/m³ for BC, 4.1 μg/m³ for O_3. Model adjusted for calendar time (time axis), sex (strata), age at baseline (strata), and region (strata); individual covariates (civil status, household size, individual wealth, family income, education, and occupational status); and area-level covariates (parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the differences of socioeconomic variables between parish and municipality, and municipality-level access to healthcare). Analysis for all-cause mortality was not stratified by regions. *N* for morbidity analysis: 2,205,956 (one was excluded due to infection before baseline). Correlation between DEHM/UBM and ELAPSE model: $PM_{2.5}$ (0.51), NO_2 (0.63), O_3 (0.47), and BC (0.47).

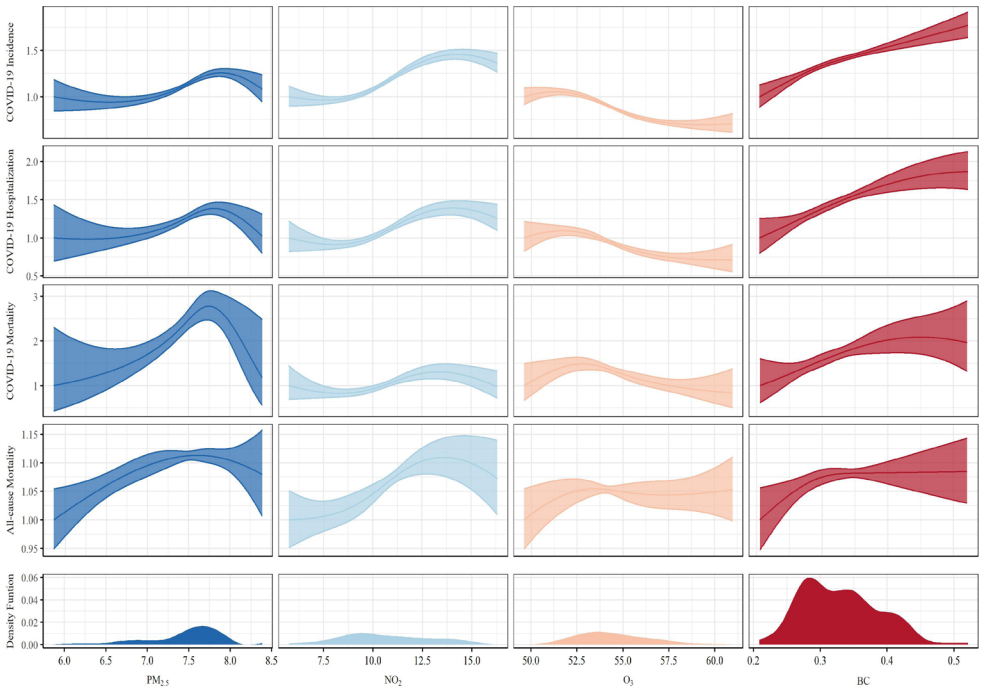

Figure 7. The shape of the associations between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 3,721,813 participants of the AIRCODEN cohort. BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; and PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 µm, respectively. Model adjusted for calendar time (time axis), sex (strata), age at baseline (strata), and region (strata); individual covariates (civil status, household size, individual wealth, family income, education, and occupational status); and area-level covariates (parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the differences of socioeconomic variables between parish and municipality, and municipality-level access to healthcare). Analysis for all-cause mortality was not stratified by regions.

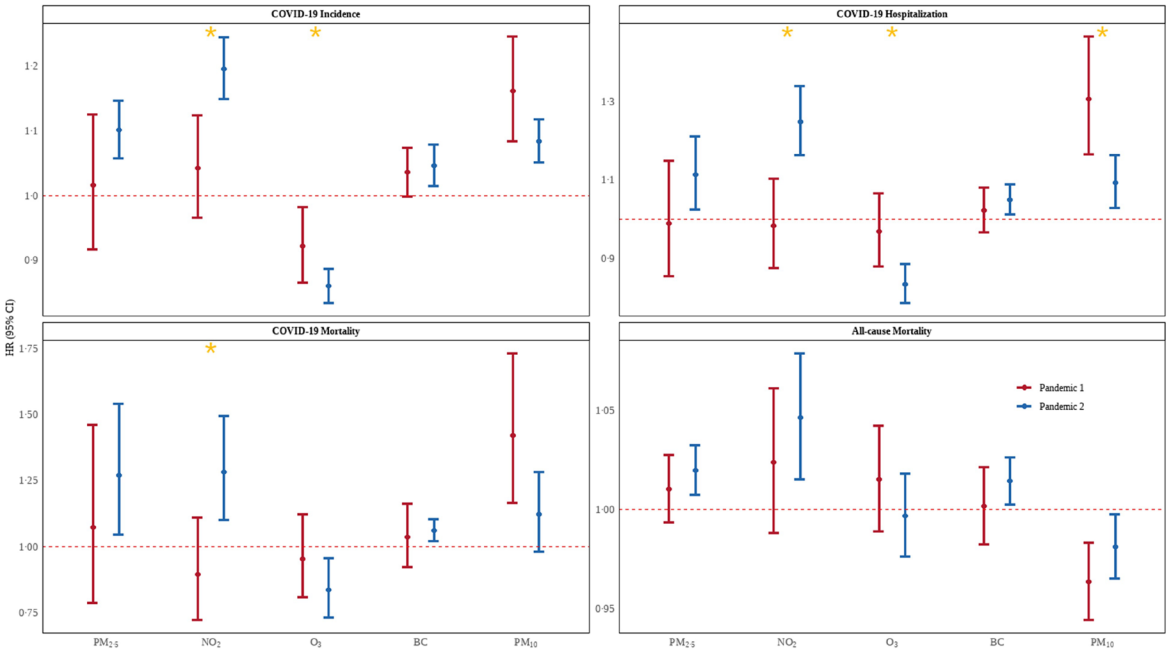

Figure 8. The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, mortality, and all-cause mortality among the 3,721,813 participants of the AIRCODEN cohort in two pandemic waves: March 1–July 31, 2020 (red) and August 1, 2020–April 26, 2021 (blue). HR = hazard ratio; CI = confidence interval; BC = black carbon; NO_2 = nitrogen dioxide; O_3 = ozone; and PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 µm, respectively. Results are presented for IQR increase: 0.55 µg/m³ for $PM_{2.5}$, 3.49 µg/m³ for NO_2, 0.09 µg/m³ for BC, 2.79 µg/m³ for O_3, and 1.14 µg/m³ for PM_{10}. Cochran's Q test were used to examine the statistical difference for the HRs observed in two pandemic waves, and results with *P* value <0.05 are highlighted with a star. Number of cases in the two pandemic waves: COVID-19 incidence (P1 = 10,480, P2 = 128,262); COVID-19 hospitalization (P1 = 2,362, P2 = 8,908); COVID-19 mortality (P1 = 636, P2 = 1,921); and all-cause mortality (P1 = 22,028, P2 = 40,331), where P1 is first pandemic wave and P2 is second pandemic wave.

with prior chronic respiratory diseases (asthma and chronic obstructive pulmonary disease), and most pronounced in those with prior acute lower respiratory infections, including pneumonias and influenza. We notably found no associations with COVID-19 in lung cancer patients. Finally, we found stronger associations in dementia and diabetes patients, which were most pronounced for NO_2 (Figure 10). The results for effect modification analyses were almost identical for COVID-19 hospitalization (Appendix Figures A3 and A4), and similar for mortality, although limited by small number of cases (Appendix Figures A5 and A6).

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19 HOSPITALIZATION AND MORTALITY AMONG COVID-19 CASES

Among 138,742 individuals who have tested positive for COVID-19, we detected positive association with COVID-19 hospitalizations (N = 11,270), with OR and 95% CIs of 1.04 (CI: 1.01–1.08) per 0.5-μg/m³ increase in $PM_{2.5}$ and 1.06 (CI: 1.01–1.12) per 3.6-μg/m³ increase in NO_2, and none with PM_{10}, BC, or O_3 (**Table 5**). These associations with risk of severe COVID-19 among those who contracted SARS-CoV-2 were notably weaker than those detected with risk of contracting COVID-19 in total population (Appendix Figure A7). We found no associations between any of the pollutants and COVID-19 mortality, except for negative association with PM_{10}.

DISCUSSION

In this large nationwide study in Danish residents 30 years old and older, we detected strong associations between long-term exposure to $PM_{2.5}$, NO_2, BC, and PM_{10}, and risk of getting infected with SARS-CoV-2, as well as getting hospitalized or dying from COVID-19. We found that those aged 65 years or older and individuals with major chronic cardiovascular and respiratory diseases, diabetes, dementia, and prior acute lower respiratory infections, as well as those in lowest SES groups (unemployed, low education, wealth or income) and those living in households with more than five people, were most vulnerable to the harmful effects of air pollution. We also found that long-term exposure to air pollution in those who were infected with COVID-19 moderately increased risk of subsequent hospitalization, but not death.

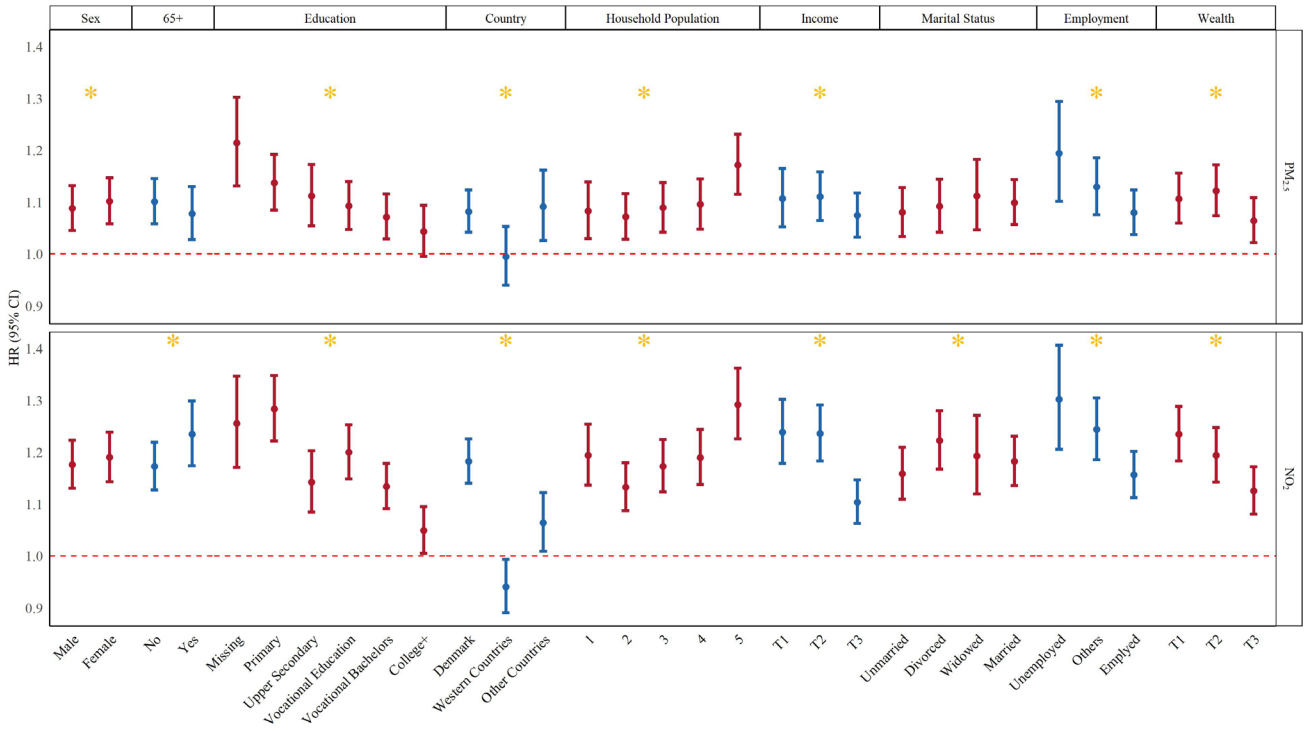

Figure 9. Effect modification of the association between long-term exposure to air pollution and COVID-19 incidence among the 3,721,810 participants of the AIRCODEN cohort by sex, age, and individual-level SES characteristic at the cohort baseline on March 1, 2020. HR = hazard ratio; CI = confidence interval; NO_2 = nitrogen dioxide; and $PM_{2.5}$ = particulate matter with diameter ≤2.5 μm. Results are presented for IQR increase: 0.55 μg/m³ for $PM_{2.5}$ and 3.49 μg/m³ for NO_2. Wald test was used to calculate the global P value, and results with P value <0.05 are highlighted with a star.

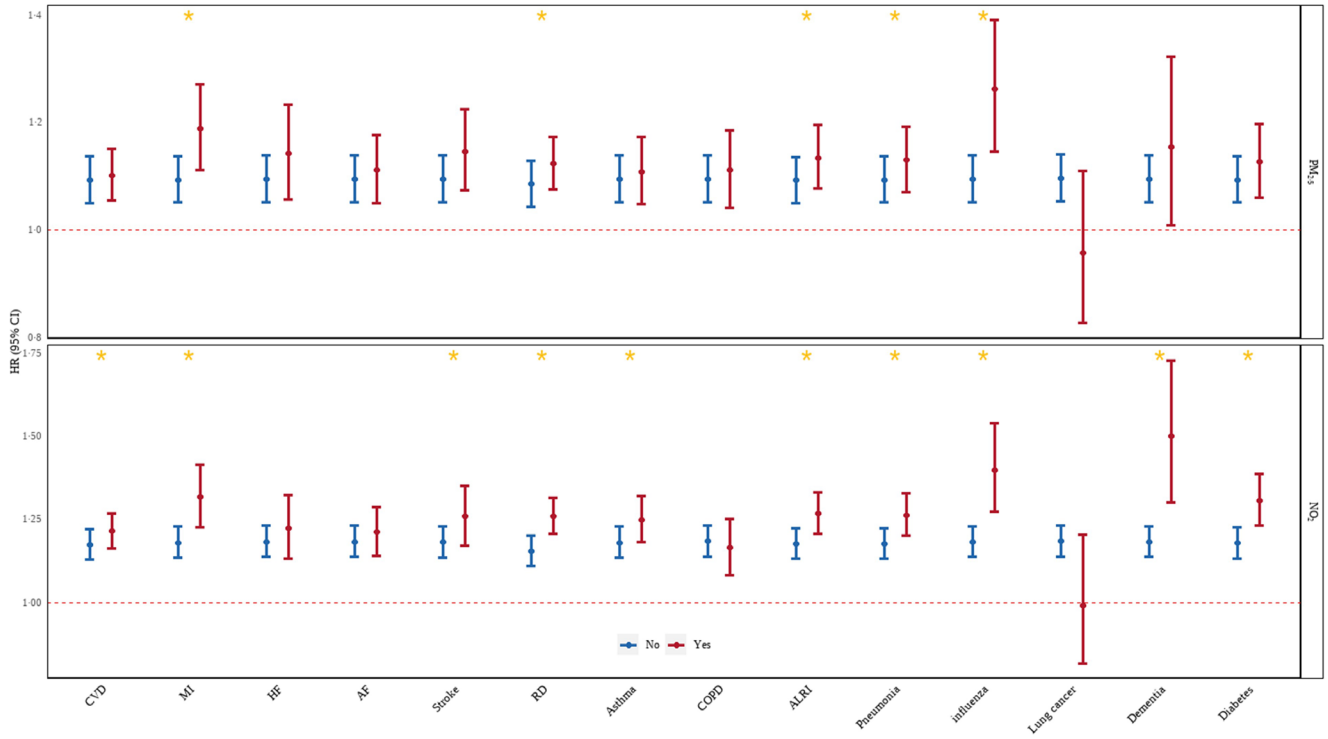

Figure 10. Effect modification of the association between long-term exposure to air pollution and COVID-19 incidence among the 3,721,810 participants of the AIRCODEN cohort by comorbidities at the cohort baseline on March 1, 2020. HR = hazard ratio; CI = confidence interval; NO_2 = nitrogen dioxide; $PM_{2.5}$ = particulate matter with diameter ≤2.5 μm; CVD = cardiovascular disease; MI = myocardial infarction; HF = heart failure; AF = atrial fibrillation; RD = respiratory disease; COPD = chronic obstructive pulmonary disease; ALRI = acute lower respiratory infections. Results are presented for IQR increase: 0.55 μg/m³ for $PM_{2.5}$ and 3.49 μg/m³ for NO_2. Wald test was used to calculate the global *P* value, and results with *P* value <0.05 are highlighted with a star.

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19 INCIDENCE, HOSPITALIZATION, AND MORTALITY

Our findings generally agree with three other studies on long-term exposure to air pollution and COVID-19 incidence, hospitalization, or mortality (**Table 6**), all of which report associations with air pollution, though with somewhat inconsistent findings on which COVID-19 outcomes were found to be related to air pollution (Kogevinas et al. 2021; Nobile et al. 2022; Sheridan et al. 2022; Veronesi et al. 2022). Our results corroborate those of Veronesi and colleagues who, in a study of 62,848 residents of Varese (of whom 4,408 tested positive for COVID-19 in the first year of the pandemic) detected 5.1% and 2% increases in COVID-19 rate for each unit (μg/m³) increase in $PM_{2.5}$ and NO_2, respectively (Veronesi et al. 2022). In 424,721 subjects from the UK Biobank (of whom tested 10,790 positive between March 16 and December 31, 2020), Sheridan and colleagues detected OR of 1.05 and 1.05 for COVID-19 incidence for each 1.3- and 9.9-μg/m³ increase in $PM_{2.5}$ and NO_2, respectively, but in contrast to our study, found no associations with COVID-19 hospitalizations (*N* = 1,598) or deaths (*N* = 568) (Sheridan et al. 2022). In 1,594,308 subjects from Rome (of whom 79,976 tested positive and 2,656 died from COVID-19 between January 1, 2020 and April 15, 2021), Nobile and colleagues have, on the other hand, found no associations with COVID-19 incidence, but reported 8% and 9% higher risk of dying from COVID-19 for each 0.92- and 9.22-μg/m³ increase in $PM_{2.5}$ and NO_2, respectively (Nobile et al. 2022). Furthermore, our results agree with those of Kogevinas and colleagues, who also found associations with COVID-19 risk assessed in detail in a smaller sample of subjects, by blood serum tests, self-reports, hospitalizations, and death (Kogevinas et al. 2021). Our finding of stronger associations of $PM_{2.5}$ and PM_{10} with increasing severity of COVID-19 outcomes was also observed by Kogevinas and colleagues (Kogevinas et al. 2021) and Nobile and colleagues (Nobile et al. 2022) but not by Sheridan and colleagues (Sheridan et al. 2022).

We detected very strong associations with COVID-19 — 10% increase in incidence and 23% in COVID-19 mortality per 0.55-μg/m³ increase in $PM_{2.5}$ — which was substantially stronger than those observed in the abovementioned studies, but in line with early findings of very strong associations with COVID-19 in general in literature and in early ecological

Table 5. The Association Between Long-Term Exposure to Air Pollution and COVID-19 Hospitalization, and Mortality Among the 138,742 Participants with COVID-19 Infection in the AIRCODEN Cohort[a,b]

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
COVID-19 Hospitalization (*N* = 11,270)			
$PM_{2.5}$	**1.06 (1.03–1.09)**	**1.05 (1.02–1.08)**	**1.04 (1.01–1.08)**
NO_2	**1.10 (1.06–1.13)**	**1.06 (1.03–1.09)**	**1.06 (1.01–1.12)**
BC	1.04 (1.02–1.07)	1.02 (1.00–1.05)	1.01 (0.97–1.05)
O_3	0.93 (0.90–0.96)	0.96 (0.93–0.99)	0.98 (0.94–1.02)
PM_{10}	0.96 (0.93–0.99)	0.95 (0.92–0.98)	0.97 (0.94–1.00)
COVID-19 Mortality (*N* = 2,557)			
$PM_{2.5}$	1.00 (0.94–1.06)	0.98 (0.93–1.04)	0.95 (0.89–1.01)
NO_2	1.12 (1.05–1.19)	1.07 (1.00–1.15)	1.02 (0.92–1.14)
BC	1.07 (1.02–1.12)	1.05 (1.00–1.11)	1.03 (0.95–1.10)
O_3	0.93 (0.87–0.98)	0.96 (0.90–1.02)	1.03 (0.94–1.12)
PM_{10}	0.85 (0.80–0.90)	0.83 (0.78–0.89)	0.86 (0.80–0.92)

HR = hazard ratio; CI = confidence interval; BC = black carbon; NO_2 = nitrogen dioxide; O_3 =ozone; PM_{10} and $PM_{2.5}$ = particulate matter with diameter ≤10 and ≤2.5 μm, respectively.

[a] Results are presented for: 0.55 μg/m³ for $PM_{2.5}$, 3.49 μg/m³ for NO_2, 0.09 μg/m³ for BC, 2.79 μg/m³ for O_3, and 1.14 μg/m³ for PM_{10}. Boldfaced text indicates statistically significant values.

[b] Model 1 adjusted for calendar time trend (natural spline with 8 degrees of freedom), sex, age at baseline (5-year bands); Model 2 additionally adjusted for civil status, household size, individual wealth, family income, education, and occupational status; Model 3 further adjusted for parish-level population density, mean income, median wealth, unemployment rate, primary or low education rate, the difference of those variables between parish and municipality, and municipality-level access to healthcare.

studies (Wu et al. 2020). The estimate of risk for COVID-19 mortality in our study is 10 times greater than that observed for $PM_{2.5}$ and all-cause mortality (i.e., 23% versus 2% per 0.55 μg/m³; Table 3). This is in line with Nobile and colleagues, who also found eight times higher estimate for COVID-19 than for non–COVID-19 deaths (8% vs. 1% per 0.92 μg/m³) in Rome (Nobile et al. 2022).

These strong associations may in part be explained by the residual confounding by smoking, BMI, physical activity, alcohol use, and other lifestyle factors for which we didn't have data, and which have explained some, but not all, of the association between air pollution and COVID-19 in the UK Biobank study (Sheridan et al. 2022), which was the only study of the above that had data on smoking and other lifestyle. Furthermore, in addition to the lack of data on individual lifestyle factors, these observed strong estimates are likely at least in part explained by residual confounding due to missing adjustment for a number of other factors related to the COVID-19 pandemic, such as patterns in access to COVID-19 testing, viral spread over time and space and prevention efforts (lockdown measures, physical distancing and facial mask recommendations, adherence to mask and distancing measures, vaccinations, etc.). On the other hand, these strong associations may be real, as we have reported earlier on considerably stronger associations between long-term exposure to air pollution and all-cause mortality in Denmark: a 14.1% increase in mortality for each 5-μg/m³ increase in $PM_{2.5}$, compared with those associations observed in other European countries that were part of ELAPSE study, which ranged from a 2.1% increase in a Dutch cohort to a 7.6% increase in a Norwegian cohort (Stafoggia et al. 2022). Furthermore, we found an indication of a curvilinear exposure–response function, in line with large studies based on low-exposure to air pollution from Europe and Canada (Brauer et al. 2019; Stafoggia et al. 2022; Strak et al. 2021) and a recent meta-analyses on studies of air pollution and mortality (Chen and Hoek 2020), suggesting stronger association in lower level exposure, which would be expected in Denmark, as the location with the lowest air pollution levels among the four others located in Italy, Spain, and the United Kingdom (Kogevinas et al. 2021; Nobile et al. 2022; Sheridan et al. 2022; Veronesi et al. 2022). Furthermore, our results of strong associations with COVID-19 outcomes and all-cause mortality, based on the air pollution data estimated by the Danish model, were remarkably consistent with an alternative air pollution exposure model based on the

Table 6. Comparison of Our Results on Association Between Long-Term Exposure to Air Pollution and COVID-19 Incidence, Hospitalization, and Mortality in General Population to Those from Literature

Study Name	Pollutant and Mean Exposure	Sample Size/Population (follow-up period)	*N* Cases	Result (HR or OR [95% CI])
COVID-19 INCIDENCE				
Our study	$PM_{2.5}$: 7.4 μg/m³ NO_2: 10.7 μg/m³	3,721,813 Denmark, all residents ≥30 years (March 1, 2020 to April 26, 2021)	138,742	$PM_{2.5}$: HR 1.10 (1.05–1.14) per 0.5[a] μg/m³ NO_2: HR 1.18 (1.14–1.23) per 3.5[a] μg/m³
Veronesi et al. 2022	$PM_{2.5}$: 12.5 μg/m³ NO_2: 20.1 μg/m³	62,848 Varese residents ≥18 years (February 15, 2020 to March 13, 2021)	4,408	$PM_{2.5}$: HR 1.05 (1.03–1.07) per 1 μg/m³ NO_2: HR 1.02 (1.01–1.03) per 1 μg/m³
Sheridan et al. 2022	$PM_{2.5}$: 10.0 μg/m³ NO_2: 26.7 μg/m³	424,721 UK Biobank, 40–69 years (March 16 to December 31, 2020)	10,790	$PM_{2.5}$: OR 1.05 (1.02–1.08) per 1.3[a] μg/m³ NO_2: OR 1.05 (1.01–1.08) per 9.9[a] μg/m³
Nobile et al. 2022	$PM_{2.5}$: 14.6 μg/m³ NO_2: 31.4 μg/m³	1,594,308 Rome, all residents ≥30 years (January 1, 2020 to April 15, 2021)	79,976	$PM_{2.5}$: HR 1.01 (0.99–1.03) per 0.9a μg/m³ NO_2: HR 1.00 (0.98–1.02) per 9.2[a] μg/m³
COVID-19 HOSPITALIZATION				
Our study	$PM_{2.5}$: 7.4 μg/m³ NO_2: 10.7 μg/m³	3,721,813 Denmark, all residents ≥30 years (March 1, 2020 to April 26, 2021)	11,270	$PM_{2.5}$: HR 1.09 (1.01–1.17) per 0.5[a] μg/m³ NO_2: HR 1.19 (1.12–1.27) per 3.5[a] μg/m³
Sheridan et al. 2022	$PM_{2.5}$: 9.9 μg/m³ NO_2: 26.7 μg/m³	424,721 UK Biobank, 40–69 years (March 16 to December 31, 2020)	1,598	$PM_{2.5}$: OR 1.01 (0.95, 1.09) per 1.3[a] μg/m³ NO_2: OR 1.02 (0.94, 1.11) per 9.9[a] μg/m³
COVID-19 MORTALITY				
Our study	$PM_{2.5}$: 7.4 μg/m³ NO_2: 10.7 μg/m³	3,721,813 Denmark, all residents ≥30 years (March 1, 2020 to April 26, 2021)	2,557	$PM_{2.5}$: HR 1.23 (1.04–1.44) per 0.5[a] μg/m³ NO_2: HR 1.18 (1.03–1.34) per 3.5[a] μg/m³
Sheridan et al. 2022	$PM_{2.5}$: 9.9 μg/m³ NO_2: 26.7 μg/m³	424,721 UK Biobank, 40–69 years (March 16 to December 31, 2020)	568	$PM_{2.5}$: OR 1.00 (0.89, 1.11) per 1.3[a] μg/m³ NO_2: OR 1.03 (0.90, 1.16) per 9.9[a] μg/m³
Nobile et al. 2022	$PM_{2.5}$: 14.6 μg/m³ NO_2:31.4 μg/m³	1,594,308 Rome, all residents ≥30 years (January 1, 2020 to April 15, 2021)	2,656	$PM_{2.5}$: HR 1.08 (1.03–1.13) per 0.9[a] μg/m³ NO_2: HR 1.09 (1.02–1.16) per 9.2[a] μg/m³

HR = hazard ratio; CI = confidence interval; OR = odds ratio. Our results are from Model 3.

[a]The HRs and ORs shown are for an interquartile range increase.

ELAPSE project (Figure 6). Within ELAPSE project, with this same exposure, we have previously documented strong associations of $PM_{2.5}$ with all-cause mortality in Europe in studies including Danish data (Stafoggia et al. 2022; Strak et al. 2021) and in Denmark in a recent nationwide study using ELAPSE (So et al. 2022) in line with those reported here, supporting the plausibility of our findings. Still, these large estimates of the association between air pollution and COVID-19 mortality demand some caution in interpretation until further research brings more data and clarity on the size of this association.

We have also detected strong associations with NO_2 of 18% increase in both incidence and mortality per 3.6-μg/m^3 increase, which are in line with $PM_{2.5}$ results. The associations are substantially stronger than those observed in previous studies (Nobile et al. 2022; Sheridan et al. 2022; Veronesi et al. 2022). In two-pollutant models with $PM_{2.5}$ we find indications of stronger associations with NO_2 (Appendix Table A3), which may suggest relevance of mainly traffic-dominated sources for risk of contracting COVID-19. However, both Sheridan and colleagues and Veronesi and colleagues reported that $PM_{2.5}$ was driving associations with COVID-19 incidence in two-pollutant models with NO_2, indicating that more data are needed to determine which air pollution component is most relevant for COVID-19. We are the first study to report an association with the traffic-related pollutant BC and COVID-19. Our results showing a strong association of PM_{10} with COVID-19 incidence were in agreement with Veronesi and colleagues (Veronesi et al. 2022), but in contrast to Sheridan and colleagues, who found no association of COVID-19 incidence, hospitalizations, or death with PM_{10} (Sheridan et al. 2022). Our finding of negative associations with O_3 are in line with Veronesi and colleagues, the only other study on COVID-19 incidence with data on O_3 (Veronesi et al. 2022), as well as with negative associations of O_3 with all-cause mortality observed in European studies (Stafoggia et al. 2022; Strak et al. 2021) and other Danish studies, both with the Danish DEHM/UBM model (Raaschou-Nielsen et al. 2020) and ELAPSE model (So et al. 2022).

Who Is Most Susceptible?

We present novel results indicating increased vulnerability to air pollution with respect to risk of developing COVID-19 of those with lowest SES. These findings likely partially capture indirectly impact of lifestyle factors associated with low SES, such as smoking, obesity, and low physical activity, for which we did not have data in this study, but which have been linked with increased risk of COVID-19. In addition, individuals with lower SES were likely more exposed to COVID-19, as they are more likely to work in occupations that were exempt from lockdown and working from home, such as cleaning workers, service workers in supermarkets, bus drivers, security workers, etc. We present novel results on enhanced vulnerability to air pollution among those living in large households, with at least five inhabitants, also related to higher risk of infection and/or higher doses of virus. We also present results of vulnerability in older people and people with chronic diseases. Veronesi and colleagues is the only study that has considered effect modification of association between $PM_{2.5}$ and risk of COVID-19 by a number of clinical conditions, and found no significant associations with any of them, but acknowledged lack of statistical power and low number of cases. Veronesi and colleagues did notably find indications of stronger associations of $PM_{2.5}$ with COVID-19 incidence in coronary heart disease and obstructive lung disease patients, which were in line with our findings (Veronesi et al. 2022). For individuals with major chronic diseases that have previously been linked to air pollution an increased susceptibility to the harms of air pollution of makes biological sense because air pollution has been linked to increased risk of the vast majority of these diseases.

Association Between Long-Term Exposure to Air Pollution and COVID-19 in Different Waves of the Pandemic

We found that associations of air pollution with COVID-19 were strongest and limited to the second pandemic wave (Figure 8). The two pandemic waves in Denmark were substantially different and comparison of the results from the two demands some caution. The second pandemic wave was the period when testing capacity was considerably higher than in the first wave, resulting in much a higher incidence rate, whereas hospitalization and death rates were more comparable in two waves, though still higher in the second wave. These differences are explained by the different phases of COVID-19 prevention measures and differences in personal behavior and lifestyle. The second pandemic wave in Denmark was characterized by a large improvement in testing capacity (testing was offered only to those with severe symptoms in the first wave) and tests were free of charge to all, by the introduction of masks, and by the reopening of society (e.g., opening of work places, restaurants, theaters, and cinemas conditional on a negative test result). These differences imply that only very limited subset of COVID-19 cases was detected in the first pandemic wave — those who traveled to Denmark from hot spot areas abroad (e.g., the ski areas in Italy and the countries of Austria and China) early in the pandemic, those presenting serious symptoms, and close contacts (family) to those infected. It is likely that these infections were not driven by air pollution. These were early cases from early phases of pandemic, in a completely closed society, and these early clusters of infection of highly new infectious virus were likely spreading by other mechanisms, mainly close contact. In contrast, in the second wave, when society had completely reopened and testing was introduced for all, virus infection took its natural course and many more people were infected, and a fraction of these infections seemed to be driven by compromised immunity associated with air pollution. Another likely explanation may be found in the COVID-19 variant, as the delta variant dominated the second wave. However, two studies from Italy (Nobile et al. 2022; Veronesi et al. 2022) report consistent associations across different pandemic

waves, notably with much poorer testing capacity in Italy and incidence definitions that differed from our study. Still, some caution in interpreting our results is needed, and more data and research is needed to confirm these possible explanations for our findings.

LONG-TERM EXPOSURE TO AIR POLLUTION AND COVID-19 HOSPITALIZATION AND MORTALITY AMONG COVID-19 CASES

Our finding of an association between long-term exposure to air pollution and COVID-19 prognosis in COVID-19 patients in terms of hospitalization risk, but not mortality, generally agrees with four other studies in COVID-19 patients, all from the United States (Bowe et al. 2021; Bozack et al. 2022; Chen et al. 2022; Mendy et al. 2021). In a study of 169,102 U.S. military veterans who tested positive for COVID-19, Bowe and colleagues detected a 10% higher risk of hospitalization (N = 25,422, followed from March 2, 2020 to January 31, 2021) for each 1.9-μg/m^3 increase in $PM_{2.5}$ (Bowe et al. 2021). In a study of 14,783 COVID-19 patients diagnosed at the University of Cincinnati healthcare system, of whom 13.6% were hospitalized between March 13 and September 30, 2020, Mendy and colleagues detected an 18% increased risk of hospitalization for each 1-μg/m^3 increase in $PM_{2.5}$ (Mendy et al. 2021). In a study of 74,915 individuals who received COVID-19 diagnoses from Kaiser Permanente Southern California between March 1 and August 31, 2020, Chen and colleagues detected a 24% higher risk of hospitalization (N = 4,752), a 32% higher risk for intensive care unit admission (N = 1,125), a 33% higher risk of intensive respiratory support (N = 1,125), and a 14% higher risk of death (N = 1,107) for each 1.5-μg/m^3 increase $PM_{2.5}$ (Chen et al. 2022). Our finding of a 4% increase in risk of hospitalization per 0.5-μg/m^3 increase $PM_{2.5}$ agrees rather well with these studies — slightly stronger than those presented by Bowe and colleagues and somewhat weaker than those presented in Mendy and colleagues and Chen and colleagues. In a slightly different approach, Bozack and colleagues studied 6,524 COVID-19 patients admitted to one of the seven New York City hospitals between March 8 and August 30, 2020. They reported an 11% higher risk of dying and a 13% higher risk of intensive care unit admission for each 1-μg/m^3 increase $PM_{2.5}$ and no association with NO_2 or BC (Bozack et al. 2022). Findings from our and previous studies on this topic provide solid support for the idea that air pollution likely increases the severity of the COVID-19 in COVID-19 patients. Notably, observed associations of air pollution with the severity of COVID-19 in COVID-19 patients are weaker than those for air pollution and risk of COVID-19 in the general population. This may indicate that long-term exposure to air pollution, captured here by exposure in 2019, increases risk of contracting COVID-19, but is a weaker determinant of COVID-19 prognosis in terms of risk of hospitalization and not a determinant of survival from COVID-19 in COVID-19 patients. This may be so because long-term exposure to air pollution based on mean pollution in 2019 does not capture relevant air pollution exposure window, which may be more relevant for prognosis of COVID-19 in the COVID-19 patients' risk of hospitalization or deaths within weeks. This risk may be better captured by more short-term exposure (months, weeks, days after COVID-19 infection), which may be more likely relevant for the potential mechanism for air pollution impact on prognosis, via compromised immunity responses. Another explanation is merely that other factors play more important roles for COVID-19 prognosis than air pollution, such as comorbidities, genetics, lifestyles, and access to treatment. Finally, another plausible explanation is collider or selection bias in analyses of COVID-19 patients — a group selected on exposure of interest and outcomes (higher air pollution exposure and more severe COVID-19 outcomes) — due to higher prevalence of comorbidities, low SES, etc., which may bias results toward null (Griffith et al. 2020). Griffith and colleagues discuss intrinsic difficulties and inference of studies of COVID-19 determinants based on COVID-19 patients.

BIOLOGICAL PLAUSIBILITY

Although the exact molecular mechanisms by which exposure to PM and gaseous pollutants affects viral infection and pathogenesis of COVID-19 remain unknown, there are a number of plausible pathways that can account for this association (Woodby et al. 2021). Apart from the direct impact of air pollution on immune responses, air pollution also likely increases risk of COVID-19 severity and death indirectly by increasing risk of related comorbidities (respiratory, cardiovascular, and metabolic diseases) which then increases risk of severe outcomes in COVID-19 patients. This may explain very strong associations between air pollution and COVID-19, observed in our study and others, as well as stronger associations with increasing severity of COVID-19 outcomes. Notably, in this study we were able to examine long-term exposure to air pollution assessed as the annual mean of pollutant concentration in 2019 and the accumulated exposure over 3 and 10 years before 2020, and we detected associations with all three exposure windows. This long-term exposure is likely to reflect and favor the postulated mechanism that air pollution increases risk of COVID-19 by increasing risk of comorbidities with cardiometabolic and respiratory diseases. We did not have data of shorter or more recent exposure windows, those of days, weeks, or months prior to SARS-CoV-2 infection, which are likely to be most relevant for the mechanism of the direct impact of air pollution on immune system and for the increased risk of contracting infection due to air pollution–related compromised immunity. Thus, we concluded that most likely our analyses and results give support for the mechanisms of air pollution impact on COVID-19 incidence, hospitalization, and mortality via an accumulated effect of air pollution over many years and increased risk of a number of chronic diseases, which in turn increase risk of COVID-19.

STRENGTHS

Our study is the largest to date and the first nationwide

analyses of associations between long-term exposure to air pollution and risk of COVID-19, facilitated by the internationally unique access to high-quality individual-level Danish COVID-19 surveillance data for an entire population. Furthermore, as Denmark had one of the most intense testing strategies and testing was offered free of charge, we were arguably, especially in the second wave of pandemic, able to determine the most complete definition of incidence of SARS-CoV-2, as more than 80% of the population was tested several times per month in the first 14 months of the pandemic. Secondly, we benefited from detailed data on disease history, which allowed us to study effect modification by comorbidities, and from a number of SES factors and data at individual and parish-level, population density, and household size, allowing for an extensive adjustment for SES factors. In addition, we benefited from data on air pollution exposure at the level of residences in 2019 and historically for 10 years prior to the pandemic, which allowed us to examine the effect of different exposure windows on COVID-19. We showed that detected associations of air pollution with COVID-19 were strong, and robust to adjustment for a number of factors as well as different air pollution assessment approaches, confirming that observed associations are likely to be real. Furthermore, as the first study to date, we benefited from data that allowed us to create monthly SARS-CoV-2 positivity rates for each municipality, by which we could capture at least some of the spatiotemporal development of the epidemic (Appendix Table A4). When conducting time-varying analyses (by splitting follow-up time in months), we found that accounting for epidemic development resulted in only a slight attenuation of the effect estimates as compared with those from our main modeling approach, the fixed-time Cox model. This result indicates that the association of long-term exposure to air pollution with COVID-19 is not confounded by the spatiotemporal patterns in pandemic development (Appendix Table A4).

LIMITATIONS

Our study has several limitations. First, we lack data on a number of possibly relevant confounders. We lack data on individual-level lifestyle factors, such as smoking, physical activity, BMI, diet, and alcohol use, which are related to air pollution and risk of contracting COVID-19. Another major limitation in our analyses is lack of data on patterns of access to COVID-19 testing, treatment, prevention efforts (such as physical and social distancing), vaccination status, mask recommendations and mask use, adherence to self-isolation, and viral spread that might be associated with air pollution. We did show that adjustment for municipality-level monthly COVID-19 positivity rates did not affect our main estimates. Still, it is likely that our very strong estimates of association between air pollution and COVID-19 incidence and mortality may be in part explained by residual confounding by a number of these missing confounders.

Another limitation is the lack of data on residence in nursing homes, where a number of countries experienced extreme high rates of COVID-19 infection and mortality. We could not address this and could therefore not make sensitivity analyses excluding nursing home residents. Notably, there was no record of heightened mortality in nursing homes in Denmark as was seen elsewhere. Furthermore, it is considered that Denmark is one of the countries that has managed COVID-19 pandemic extremely well, without any excess mortality in 2020, and without COVID-19 mortality clusters in nursing homes. Still, it is possible that some of our high effect estimates may be explained by a strong association between air pollution and COVID-19 in nursing homes.

The Danish COVID-19 surveillance system, especially in the early stages of the pandemic, could only identify a selected sample of all infected individuals, for example, those with severe symptoms, close contacts of primary cases with symptoms, and those who were hospitalized for other causes, and were thus tested routinely. The testing policy was massively expanded in the second wave, from around August 2020 and onward, when testing free of charge was offered to all Danish residents. This has resulted in a large portion of population being tested daily, as a negative test result was required to enter workplaces, universities, schools, restaurants, movie theaters, theaters, sport facilities, and public transport. Therefore, our definition of SARS-CoV-2 incidence is only partial, especially in the first wave. Consequently, the definition of COVID-19 in two phases of the pandemic differ substantially and thus, results on air pollution association with COVID-19 cannot be directly compared in two waves. We did show, however, that our results were unchanged when limiting the study population to those who were tested, comprising 78% of total population (Appendix page 6), suggesting that the selection of the population who was tested was not related to air pollution exposure.

Challenges specific to studying COVID-19 incidence include accurate identification of cases, as well as potential or differential errors in case ascertainment for different population groups. Identification of incident cases depends on a number of factors including voluntary participation in testing, the testing capacity and accessibility, the cost of testing, test accuracy, symptom severity and recognition in the case where testing is offered only to those with certain symptoms or certain symptom severity (e.g., in the first wave of the pandemic in our study and in many countries with more limited testing capacity than Denmark). Furthermore, high rates of asymptomatic virus carriers, as well as cases with atypical symptom presentation, both of which depend on COVID-19 variant and change over time, further complicate the accurate ascertainment of COVID-19 incident cases. We must also acknowledge differential errors in ascertainment for different population groups, by occupation, SES, ethnicity, place of residence and social connectedness, frailty, internet access and technological engagement, and medical and scientific interest. Certain occupations, such as healthcare workers, are far more likely to be tested, and will be overrepresented in incidence ascertainment. Similarly, frail people, such as people who are older, obese, have major chronic diseases, or

are nursing home residents, as well as possibly smokers, are also tested more. People with better access to healthcare and testing facilities, those with awareness and access to information, skills to use internet apps used for booking testing or checking results, as well as those with strong medical and scientific interest will be more likely to be tested (Griffith et al. 2020). In any case, in this study, we must acknowledge the limitation of defining COVID-19 hospitalization or death as any such event that occurred within a period after first diagnosis, rather than an official primary cause of that hospitalization or death. We must also acknowledge that differential accuracy in ascertainment of COVID-19 cases and overrepresentation of cases for certain subgroups may have influenced our effect modification result.

We lacked data on vaccinations and could not address whether vaccination would have affected observed associations. First vaccination in Denmark was given on December 27, 2020, and only a fraction of population was vaccinated by April 26, 2021. At the end of follow-up in this study 555,236 people, or 9.5% of Danish population, were fully vaccinated, and 1,226,180 people (21% of Danish population) received first dose on April 26th, 2022 (Appendix Figure A8).

CONCLUSION

In a nationwide Danish study covering first 14 months of COVID-19 pandemic, we have found that long-term exposure to air pollution at very low levels — levels well below current EU limit values — is associated with increased risk of contracting SARS-CoV-2, as well as developing severe COVID-19 disease demanding hospitalization or resulting in death. Patients with chronic cardiometabolic, respiratory, and neurodegenerative diseases, older people, those people with prior acute lower respiratory infections, and people in the lowest SES groups are most susceptible and most likely to contract SARS-CoV-2 or develop COVID-19 associated with air pollution and need to be protected. These findings contribute important new data to an increasing evidence base showing that air pollution is a risk factor for COVID-19, adding to an overall burden of air pollution. The reduction of air pollution should be at the heart of current and future pandemic mitigation strategies, as it would provide more resilient populations to SARS-CoV-2 and similar infections.

IMPLICATIONS OF THE FINDINGS

This large nationwide study provides strong new evidence in support of association between long-term exposure to air pollution and COVID-19. These results reinforce the importance of air pollution regulation as an integral part of COVID-19 pandemic mitigation strategies, as well as for planning for future similar pandemics. Reduction of air pollution would provide for populations who are more resilient to viral respiratory infections, such as COVID-19, and likely to other viral and bacterial respiratory infections (e.g., seasonal influenza and pneumonias). Reductions in air pollution would also bring other major health benefits, in terms of prevention of major chronic noncommunicable diseases and providing for better quality of life and better disease prognosis for patients with chronic diseases, as well as in mitigating impact of climate change on health.

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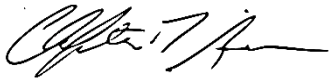
HEI QUALITY ASSURANCE STATEMENT

Eastern Research Group, Inc. (ERG) independently provided quality assurance (QA) oversight for this study. ERG staff members Dr. Clifton Dassuncao, John Wilhelmi, and Dr. Rebecca Devries conducted a remote audit of the final report. An on-site audit was not conducted for this study. The ERG auditors are experienced in QA oversight and the subject matter relevant to this study, including epidemiological methods, statistical methods, exposure assessment, air quality modeling, and health outcomes research. Dr. Dassuncao, an environmental epidemiologist, served as the lead auditor and interacted with principal investigators, reviewed R code, and reviewed all aspects of the final report. Mr. Wilhelmi, an air quality specialist, and Dr. Devries, an epidemiologist, provided additional independent reviews of the final report.

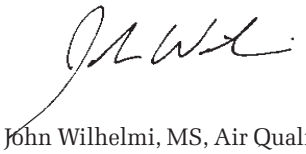
The remote audit of the final report was conducted from April through November 2023. The objectives of this audit were to ensure that study methods were well documented, the final report was understandable, reported results were accurate, and key study findings and limitations were highlighted. The audit also evaluated whether the documented study protocols were adhered to. To meet these objectives, the ERG auditors reviewed the final report text, tables, and figures to verify their accuracy and clarity. Study and QA protocols were also reviewed for consistency with reported methods. R codes documenting data processing and analysis were provided to ERG and compared to the methods and findings described in the final report. However, the researchers did not share with ERG the underlying air quality modeling data or the data on COVID-19 testing, morbidity, and mortality. The researchers noted that the COVID-19 data could not be shared due to confidentiality restrictions. Without access to these data, ERG could not reproduce any results in the final report. ERG was able to review some data processing code to verify that certain calculations were conducted consistent with described methods.

ERG auditors focused their review on the final report text and how it adhered to study protocols and documented analyses in R. Auditors identified parts of the final report text that could be improved for clarity and accuracy. Some discrepancies were identified between the report text, the R code, and study protocols; however, these discrepancies were addressed and did not alter the findings or conclusions. Auditors were unable to verify specific numerical values without access to the data to rerun analyses; however, numerical values were evaluated for internal consistency and against the R code.

Audit findings were documented in an ERG audit report and an HEI follow-up memorandum. The findings of the audit did not critically impact the overall results of this research study. Primary analyses were clearly documented in R, the overall approach was adequately described, and key results were clearly presented in tables and figures. Although ERG was not provided the data needed to reproduce results, the audit team is confident that the final AIRCODEN study report was representative of the research conducted and that the study followed a valid set of procedures documented in study protocols.



Clifton Dassuncao, MS, ScD, Environmental Epidemiologist, Quality Assurance Auditor



John Wilhelmi, MS, Air Quality Specialist, Quality Assurance Auditor

Rebecca Devries, MS, ScD, Epidemiologist, Quality Assurance Auditor

MATERIALS AVAILABLE ON THE HEI WEBSITE

Appendix A contains supplementary material not included in the main report. It is available on the HEI website at *www.healtheffects.org/publications*.

Appendix A. Supplementary Tables and Figures

ABOUT THE AUTHORS

Zorana Jovanovic Andersen is a professor from the Section of Environmental Health, Department of Public Health, at the University of Copenhagen in Denmark. Over the last 15 years, she has focused on studying health effects related to exposure to air pollution and road traffic noise, which resulted in 112 published peer-reviewed papers (21 as first, 27 as second, and 26 as last author), with a scientific impact factor of 47 (Google Scholar) and more than 9,400 citations. Andersen has documented adverse effects of air pollution in Denmark showing that long-term exposure to air pollution leads to increased risk of asthma, chronic obstructive pulmonary disease, cardiovascular disease, stroke, diabetes, lung cancer, and premature mortality in adults as well as asthma in children. Her main research findings are that — despite low levels of air pollution in Denmark complying with EU limit values — there is still significant health burden due to air pollution exposure. Her research has strengthened the evidence base for stricter air pollution regulation in the European Union. Andersen's other contributions include results showing that benefits of exercise outweigh harms related to air pollution exposure when exercising in highly polluted areas. She is also active in work with advocacy and translation of knowledge on air pollution health effects to policymakers through her role as Chair of the European Respiratory Society Environmental Health Committee, member of the Expert Group on Air Pollution in Copenhagen Municipality, member of the International Society for Environmental Epidemiology (ISEE) Policy Committee, and ISEE representative at the International Network for Epidemiology in Policy.

Jiawei Zhang is a Ph.D. fellow from the Section of Environmental Health, Department of Public Health, at the University of Copenhagen in Denmark, under the supervision of Zorana Jovanovic Andersen, Youn-Hee Lim, and Rudi G.J. Westendorp. His doctoral project focused on the association between long-term exposure to air pollution and risk of morbidity and mortality from respiratory disease with a special concentration on infectious disease, including COVID-19, pneumonia, and other lower respiratory tract infection diseases. Zhang has enrolled in several HEI-funded projects, including the ELAPSE project and the Impact of Exposure to Air Pollution on Asthma project. In the AIRCODEN project, he contributed to the cohort generation and statistical analysis.

Youn-Hee Lim is an assistant professor from the Section of Environmental Health, Department of Public Health, at the University of Copenhagen in Denmark. She investigates associations between climate change, air pollution, and endocrine-disrupting chemicals and growth and neurocognitive development in children as well as cardiovascular, metabolic, and neurodegenerative diseases in women and older populations. In addition, Lim is interested in the roles of the gene, DNA methylation, and microbiome on environmental health.

Rina So is a postdoctoral fellow from the Section of Environmental Health, Department of Public Health at the University of Copenhagen in Denmark. She obtained her Ph.D. degree from the University of Copenhagen under the supervision of Zorana Jovanovic Andersen. In her Ph.D. project, So studied the association of long-term exposure to air pollution and road traffic noise with mortality and morbidity in Denmark using the Danish Nurse Cohort and nationwide health administrative registries.

Jeanette T. Jørgensen obtained her Ph.D. degree from the Department of Public Health at the University of Copenhagen in Denmark under the supervision of Zorana Jovanovic Andersen. She has experience in register-based research from multiple Danish and international projects. Her cross-disciplinary background with an M.Sc. IT and Health has given her solid and unique analytical skills — appropriate in various parts of the research process from design and statistical programming to the interpretation and dissemination of research results. Jørgensen's research is in the field of environmental and occupational epidemiology, and her work has resulted in authorships of 18 scientific papers published in various international peer-reviewed journals.

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Thomas Cole-Hunter is an assistant professor from the Section of Environmental Health, Department of Public Health, at the University of Copenhagen in Denmark. He has broad

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Steffen Loft is a professor from the Section of Environmental Health, Department of Public Health, at the University of Copenhagen in Denmark. He researches toxicology and how the body absorbs and handles toxins. In particular, he studies the effect of particles in air pollution and is knowledgeable about the relationship between diet and cancer as well as the negative health aspects of modern industrial nanotechnology. His major recent research achievements include demonstration of effects of nanoparticles on oxidative damage to DNA and vascular functions, both in susceptible transgenic animal models and in humans, and that a number of biomarkers of exposure can predict risk of cancer in prospective settings. Loft has published over 400 scientific papers in international peer-reviewed journals in the field of toxicology.

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Gerard Hoek is an associate professor at the Institute for Risk Assessment Sciences at Utrecht University in the Netherlands. He has more than 20 years of experience in performing research in air pollution exposure assessment and epidemiology. His main research has been exposure assessment and epidemiological studies of respiratory and cardiovascular effects of short- and long-term exposure to fine and ultrafine particles. Hoek graduated in 1986 as an environmental hygienist, and in 1992 he obtained his Ph.D. degree in air pollution epidemiology (short-term respiratory health effects of outdoor air pollution in children). He has been principal investigator and senior scientist in a large number of E.U.–funded studies in the field of environmental health, and he has advised the U.S. Environmental Protection Agency (EPA), the European Union, the World Health Organization, the Health Effects Institute, and other national and international bodies. He coordinated exposure assessment and the cardiorespiratory mortality effects of outdoor air pollution in the multicenter ESCAPE study. In addition, Hoek has served as a reviewer for major biomedical and epidemiological journals and is the coauthor of more than 250 peer-reviewed papers in the fields of environmental exposure assessment and epidemiology. His recent research interests include health effects of combined exposure to air pollution, noise, and greenness as well as the development of models using mobile monitoring.

Bert Brunekreef is an emeritus professor of environmental epidemiology in veterinary medicine and medicine at Utrecht University in the Netherlands. On several occasions, he served as advisor on national and international panels in the field of environmental health, including the Dutch National Health Council (of which he is a member), the World Health Organization, and the U.S. EPA. Brunekreef is a coauthor of more than 400 peer-reviewed journal articles in the field of environmental epidemiology and exposure assessment. In recent years, he received the ISEE John Goldsmith award (2007), the European Lung Foundation Award (2007), an honorary doctorate of the Catholic University of Leuven, Belgium (2008), the Heineken Prize for Environmental Sciences (2008), and an Academy Professorship of the Dutch Royal Academy of Sciences (2009), to which he also was elected to become a member in 2009.

Rudi G.J. Westendorp is a professor of medicine of old age in the Department of Public Health at the University of Copenhagen in Denmark. He is also a codirector of the Center of Healthy Aging at the University of Copenhagen and senior scientist at Statistics Denmark. Westendorp has coauthored over 700 peer-reviewed reports that have been cited over 25,000 times. His Hirsch-index is 75+. Using analysis from Web of Science in 2012, *Lab Times* ranked him as the eighth most cited author in aging research in Europe, which includes the second most cited article from 1999 through 2010.

Matthias Ketzel is a professor in the Section of Atmospheric Modelling, Department of Environmental Science, at Aarhus University in Roskilde, Denmark, and a visiting professor at the Global Centre for Clean Air Research (GCARE) at the University of Surrey in the United Kingdom. He received his Ph.D. from Lund University in Sweden. He has a background in physics and fluid dynamics and has more than 28 years of experience in the field of atmospheric science, specifically human exposure assessment and local-scale atmospheric dispersion modeling. Ketzel's main research interest is aerosol dynamics modeling and human exposure estimation at regional, urban, and street scale with a strong focus on particles and gaseous air pollutants.

Jørgen Brandt is a professor and head of the section of atmospheric modeling and the Centre Director of iCLIMATE in the Department of Environmental Science at Aarhus University. He has an M.Sc. in geophysics and meteorology and a Ph.D. in atmospheric physics/atmospheric modelling from the Niels

Bohr Institute at the University of Copenhagen in Denmark. He has 27 years of experience in calculating air pollution levels with very high resolution over a long period for the hemispheric, regional, national, and urban background scales. He has been leading the development of an integrated multiscale model system (THOR), including all scales from the Northern Hemisphere, European scales, national scales, urban background, and street canyon. Results from THOR have already been applied with success in epidemiological research.

Theis Lange is the vice head of the Department of Public Health at the University of Copenhagen in Denmark. His research involves theoretical research within statistics as well as a wide range of applied collaborations with medical doctors, epidemiologists, and psychologists. His theoretical work is focused on causal inference (i.e., a formal framework for addressing cause and effect methods he has developed), which has been broadly applied and whose novelty was recognized by the 2012 Kenneth Rothman Prize (the underlying paper has been cited 190 times). His applied collaborations span from randomized controlled trials to complex longitudinal observational studies and from intensive care research to psychology; in total, he has published 142 papers (total number of citations 3,084; h-index 30). Since being awarded the EliteForsk travel grant of 250,000 DKK during his Ph.D., Lange has been principal investigator and co-principal investigator for successful grant applications totaling 120 million DKK. Until the summer of 2019, he held a dual position in the Section of Biostatistics at the University of Copenhagen and the Center for Statistical Science at Peking University. Lange has served on the Danish Heart Association and Statistics Denmark research boards and has been working for BeiGene as their senior statistical methodology expert (BeiGene is a Chinese pharmaceutical company working on novel oncology treatments).

Thea Kølsen Fischer is a medical doctor with a D.M.Sc. (Ph.D.) in virology and infectious disease epidemiology and a medical specialization in public health. She has a clinical background in infectious diseases, was trained in epidemic response and preparedness at the U.S. Centers for Disease Control and Prevention, and has conducted worldwide research in the interdisciplinary field of virus epidemics and prevention for over 20 years. Kølsen Fischer currently serves as an adjunct professor at the University of Southern Denmark in Global Health and Infectious Diseases. In 2019, she was invited to write reviews for *Emerging Infectious Diseases, The New England Journal of Medicine, The Lancet Infectious Diseases,* and *Eurosurveillance*.

OTHER PUBLICATIONS RESULTING FROM THIS RESEARCH

Zhang J, Lim Y-H, So R, Jørgensen JT, Mortensen LH, Napolitano GM, et al. 2023. Long-term exposure to air pollution and SARS-CoV-2 infection and COVID-19 hospitalisation or death: Danish nationwide cohort study. Eur Respir J 62:2300280; doi:10.1183/13993003.00280-2023.

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.

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

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.

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).

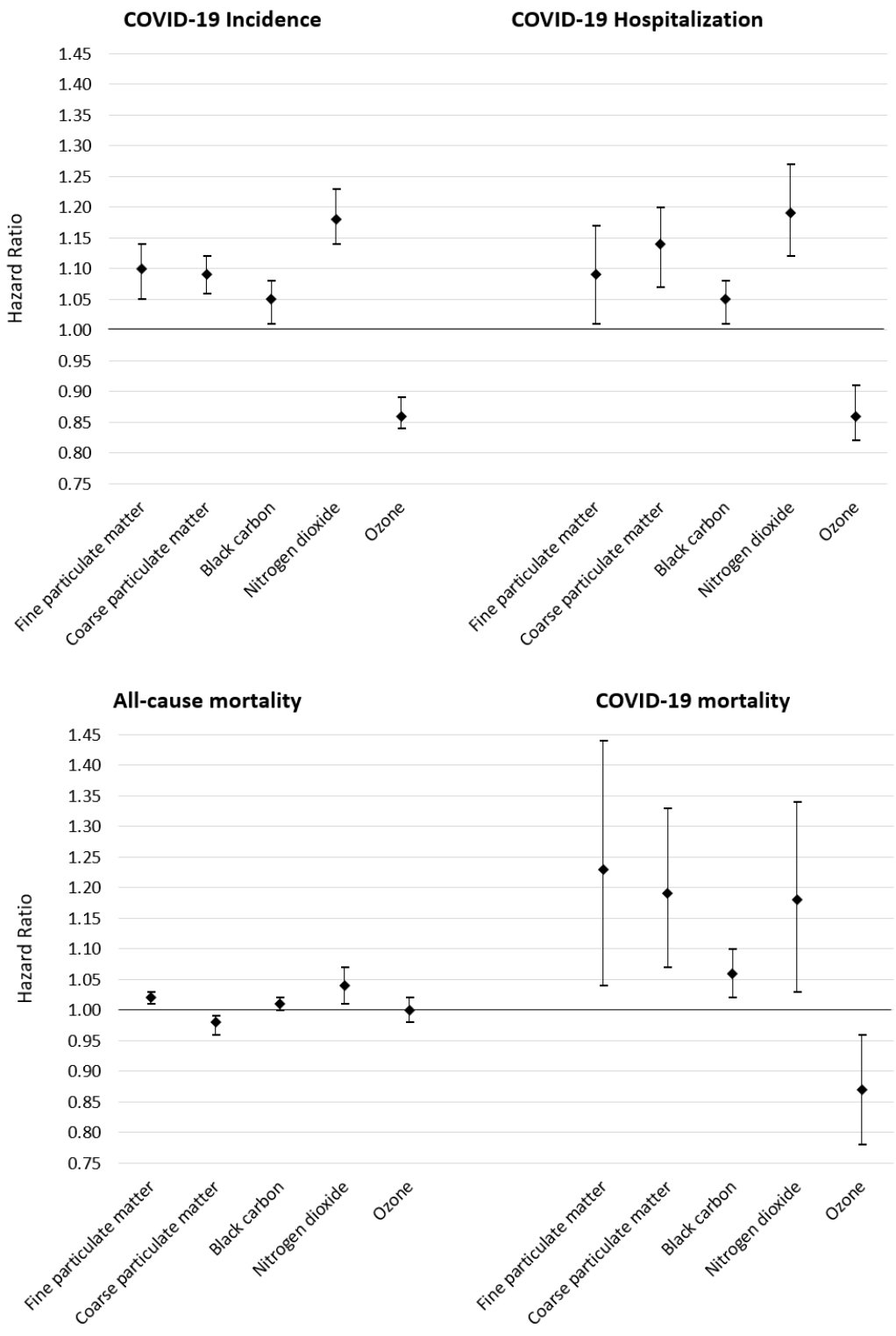
EPIDEMIOLOGICAL RESULTS

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



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/m³ for $PM_{2.5}$, 1.14 μg/m³ for PM_{10}, 0.09 μg/m³ for BC, 3.49 μg/m³ for NO_2, and 2.79 μg/m³ for O_3. Results are from the analyses using all available individual- and contextual-level variables (Model 3). (Source: Investigators' Report Table 3.)

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 TERMS

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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