Report

Long-term exposure to air pollution and COVID-19 mortality and morbidity in Copenhagen, Denmark

Zorana Jovanovic Andersen[a], Jiawei Zhang[a], Youn-Hee Lim[a], Laust H. Mortensen[b,c], George M. Napolitano[a], Thomas Cole-Hunter[a], Steffen Loft[a], Gerard Hoek[d], Bert Brunekreef[d], Theis Lange[h]

Affiliations:
[a]Section of Environmental Health, Department of Public Health, University of Copenhagen, Copenhagen, Øster Farmiagsgade 5, 1353 Copenhagen, Denmark;
[b]Section of Epidemiology, Department of Public Health, University of Copenhagen, 1353 Copenhagen, Denmark;
[c]Statistics Denmark, Copenhagen, Denmark;
[d]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands;
[e]Department of Public Health, University of Copenhagen, Copenhagen, Øster Farmiagsgade 5, 1353 Copenhagen, Denmark;

Contact address: Zorana Jovanovic Andersen, Section of Environmental Health, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1353 Copenhagen, Denmark. E-mail: zorana.andersen@sund.ku.dk; Phone number: +4520740462.

TABLE OF CONTENTS

FIGURES

TABLES

APPENDIX:
FIGURE

TABLE

ABBREVIATIONS AND OTHER TERMS

AQG	Air Quality Guidelines
AirGIS	A Geographical Information Systems based air pollution and human exposure modelling system
COVID-19	Coronavirus Diseases 2019
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Air Pollution Effects
GBD	Global Burden of Disease
HEI	Health Effects Institute
HR	Hazard Ratio
ICD	International Classification of Diseases
IQR	Interquartile Range
NO_2	Nitrogen Dioxide
NO_X	Nitrogen Oxides
O_3	Ozone
OR	Odds Ratio
$PM_{2.5}$	Particulate matter with an aerodynamic diameter < 2.5 µm
PM_{10}	Particulate matter with an aerodynamic diameter < 10 µm
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SES	Socio-Economic Status
TRAP	Traffic-Related Air Pollution
UBM	Urban Background Model
WHO	World Health Organization

SUMMARY

Introduction: Early ecological studies suggested the link between air pollution and Coronavirus Diseases 2019 (COVID-19). However, the evidence from individual-level prospective cohort studies with data on chronic exposure to air pollution and COVID-19 outcomes, such as incidence, hospitalization, and death, are still few. Here, we have examined whether long-term exposure to air pollution is associated with risk of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and developing severe COVID-19 resulting in hospitalization or death in Copenhagen. We have also examined who is most susceptible to harmful effects of air pollution by age, sex, socio-economic status (SES) and co-morbidities.

Methods: We have created an AIRCODEN-CPH cohort including all residents 50 years or older and residing in Copenhagen, Frederiksberg, or Tårnby municipalities on March 1, 2020. We followed AIRCODEN-CPH participants in the National COVID-19 Surveillance System until the date of 1st positive test (incidence), COVID-19 hospitalization, COVID-19 death, or death from any cause until April 26, 2021. We have estimated mean levels of particulate matter < 2.5 µm in diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3) at cohort participants' residence in 2019 by the Danish DEHM/UBM model. We used Cox proportional hazard models to estimate the associations of air pollutants with COVID-19 incidence, hospitalization, mortality and all-cause mortality, adjusting for age, sex, individual- and area-level socioeconomic status (SES). We examined effect modification of the association between $PM_{2.5}$ and NO_2 and COVID-19 incidence, hospitalization, and mortality by age, sex, SES (education, income, employment), and co-morbidities (prevalence on March 1, 2020) with cardiovascular disease, respiratory disease, acute lower respiratory infections, diabetes, lung cancer, and dementia.

Results: Of 192,041 people incuded in the study, 10,324 were infected, 1,563 hospitalized and 461 died from COVID-19 during 14 months of follow-up. We detected positive associations with COVID-19 incidence, with hazard ratio and 95% confidence interval of 1.04 (1.00-1.07) per 2.67 µg/m^3 increase in $PM_{2.5}$, 1.02 (1.00-1.04) per 6.25 µg/m^3 increase in NO_2, and 1.04 (1.02-1.07) per 0.35 µg/m^3 increase in BC. Corresponding HRs and 95% CIs for COVID-19 hospitalizations were 1.11 (1.02-1.21), 1.03 (0.98-1.08), and 1.06 (1.00-1.12), and for COVID-19 death 1.09 (0.93-1.28), 0.97 (0.88-1.06), and 1.01 (0.90-1.13). We found no association with O_3. Associations of $PM_{2.5}$ with COVID-19 incidence were statistically significantly stronger in elderly (65 years old or older) and with all pollutants for participants who lived in large households (5 persons or more living together), and in chronic cardiovascular and respiratory disease and diabetes patients.

Conclusions: Long-term exposure to air pollution may contribute to increased risk of contracting SARS-CoV-2 infection as well as developing severe COVID-19 disease demanding hospitalization or resulting in death. We present novel findings on the especially vulnerable groups, including elderly and chronic disease patients, as well as those with prior severe respiratory infections (pneumonia, influenza demanding hospitalization). This large study provide strong new evidence in support of causal association between 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 (seasonal influenza and pneumonias, etc.). Reductions in air pollution would also bring other major health benefits, in terms of prevention of major chronic non-communicable diseases and providing for better quality of life and better disease prognosis for chronic disease patients, as well as in mitigating impact of climate change on health.

INTRODUCTION

One of the important public health objectives in the midst of COVID-19 epidemic is to identify key modifiable factors that could contribute to increased risk of contracting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus and developing Coronavirus Diseases 2019 (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 preparing of the strategies for future similar pandemics. Air pollution is the major environmental stressor and 4th top ranked global risk factor for morbidity and mortality (after smoking, high blood pressure and poor diet) causing 6,7 million deaths in 2019, from ischemic heart disease (IHD), cerebrovascular disease, chronic obstructive pulmonary disease (COPD), acute lower respiratory infections (ALRIs), lung cancer, diabetes, and neonatal deaths (Health Effects Institute 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 (Health Effects Institute 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 particulate matter (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 is caused by direct cellular damage, and indirectly via oxidative stress and inflammation in the lung and system, that 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 few studies have examined association between long-term exposure to air pollution and pneumonia incidence or hospitalizations (Carey et al. 2016; Neupane et al. 2010; Salimi et al. 2018), with mixed results, as two report positive (Carey et al. 2016; Neupane et al. 2010) and one finds no association (Salimi et al. 2018). Based on these three studies, recent systematic review and meta-analyses from the Health Effects Institute on the associations between traffic related air pollution (TRAP) (including nitrogen dioxide (NO_2), PM with diameter < 2.5 µm ($PM_{2.5}$), and elemental carbon (EC)) and a number of health outcomes, have concluded that the confidence was very low or low for an association with TRAP and the risk of ALRIs. However, global burden of disease (GBD) study has recognized the causal link between air pollution and ALRI mortality (Health Effects Institute 2020), which is supported on 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 risk of COVID-19, despite the fallacies of such designs (Villeneuve and Goldberg 2020). An US study gained instant attention by the media in May 2020, when preliminary (non-peer-reviewed) results by Wu et al. (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 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 USA counties were compared against very crude, county-average concentrations of $PM_{2.5}$ over a 17-year period, with lack of individual-level data on exposure, outcome, and important confounders (SES, lifestyle, co-morbidities). Early studies on long-term exposure to air pollution and COVID-19 using ecological design, 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.

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/countries, and to call for careful interpretation of these early results. Following Wu et al., another nationwide US study based on the same county-level data as the study by Wu et al., but utilizing a different air pollution modeling approach, examined the long-term effect of NO_2, $PM_{2.5,}$ and ozone (O_3) on COVID-19 case fatality and mortality rates and reported a 7.1% (1.2-13.4%) and 11.2% (3.4-19.5%) increase per 4.5ppb increase in NO_2 for case fatality and mortality rate respectively (Liang et al. 2020). Notably, in contrast to Wu et al., Liang et al. 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 30th, 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% (-2.1%-5.1%) increase in the COVID-19 mortality rate for every 1 $\mu g/m^3$ increase in NO_2 and $PM_{2.5}$, respectively (Konstantinoudis et al. 2021). On the other hand, Travaglio et al. 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). Notably, Travaglio et al. have also, as the first study at the time, included individual-level data on 'infectivity' from the UK Biobank, including 1,450 tested individuals of which 699 tested positive, where they showed significant associations with $PM_{2.5}$ but none with NO_2, in contrast to their abovementioned results on regional analyses.

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 inference 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 the 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 et al. also, 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 (Travaglio et al. 2021). Only three studies examined association of long-term exposure to air pollution COVID-19 incidence in general population, defined as the first positive SARS-CoV-2 test, and they offer mixed results. Veronesi et al. have in a city-wide study in 62,848 residents of Varese, Italy, of whom 4,408 tested positive for COVID-19 in 1st year of pandemic, detected 5.1%, 2%, and 4% increase in COVID-19 rate for each $\mu g/m^3$ increase in $PM_{2.5}$, NO_2, and PM_{10}, respectively (Veronesi et al. 2022). Sheridan et al. has in 424,721 subjects from UK Biobank, of whom 10,790 tested positive between March 16 and December 31, 2020, detected associations with odds ratios (ORs) of 1.06 and 1.05 for COVID-19 incidence for each 1.3 and 9.9 $\mu g/m^3$ 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). Nobile et al. have 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, 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 $\mu g/m^3$ increase in $PM_{2.5}$ and NO_2, respectively (had not data on PM_{10}) (Nobile et al. 2022). In slightly different approach, a study by Kogevinas et al. based on 9,605 subjects from COVICAT cohort 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 et al. 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 US, 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 (ICU) admissions, or death that is related to COVID-19. All of these studies have detected association between $PM_{2.5}$ and risk of severe COVID-19 outcomes, including hospitalizations (Bowe et al. 2021; Chen et al. 2022; Mendy et al. 2021), ICU 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, with access to historical residential address data, COVID-19 deaths and hospitalization data, as well as SES and co-morbidity data at the individual level, provide 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 PCR testing, within sufficient control for confounding, and collinearity between population density and exposure. This research was designed to provide new, high quality data to support 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 COVID-19 related mortality and morbidity in Copenhagen, and to identify the most susceptible groups by age, sex, socioeconomic status (SES), ethnicity, and co-morbidities. Specific aims are:

1. Examine whether long-term exposure to $PM_{2.5}$, NO_2, black carbon (BC), and ozone (O_3) are associated with risk of contracting COVID-19, in terms of COVID-19 incidence, hospitalizations, or death.
2. Identify subgroups that are susceptible to air pollution-related COVID-19 morbidity and mortality by age, sex, SES (education, household income, occupational status, civil status, housing tenure, and household size, type and composition), ethnicity (Danish, non-western and western origin), and co-morbidity (cardiovascular disease (CVD), respiratory disease (RD), ALRIs, lung cancer, diabetes, and dementia).

METHODS AND STUDY DESIGN

Study Population

We have created a population-based Copenhagen cohort (AIRCODEN-CPH) by including all residents of Copenhagen, Frederiksberg, and Tårnby municipalities who were 50 years or older on March 1, 2020 and had lived in Denmark for at least one year prior to this date.

COVID-19 outcome definitions

Danish Statens Serum Institut (SSI), 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 centres, and SSI's own laboratory, which are collected centrally in the Danish Microbiological Database (MiBa; https://miba.ssi.dk/service/english). Data includes results from the PCR test for the COVID-19 virus. We obtained data on COVID-19 data for this from the Danish Health Data Authority, notably with a 5-month delay due to COVID-19 lockdown measures which have 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. The detailed description of the available data is provided in the Table A1 in the Appendix1. The SSI 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: SSI works continuously to improve their surveillance algorithms, which means that changes to existing algorithms can still arise. SSI publishes a log of the changes of their algorithms on their website; 2) Changes in test strategy affect population: 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 number, we have linked the AIRCODEN-CPH 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, 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 following COVID-19 outcomes: incidence (first positive PCR test for SARS-CoV-19), hospitalization (hospital admission for more than 12 hours within 14 days after the first positive PCR test for SARS-CoV-19), and death (death within 30 days of the detection of SARS-CoV-19 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 causes 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 nationwide Danish cohort from year 2000.

Covariate and co-morbidity definitions

We have extracted individual-level SES information for year 2019 from the Danish national registers with information on individual SES for all Danish citizens, including occupation, personal income and transfer payments (Baadsgaard and Quitzau 2011), personal labor market affiliation (Petersson et al. 2011), and education (Jensen and Rasmussen 2011), 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)
- Family family/household taxable 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 (smallest administrative unit in Denmark, 2,158 parishes in Denmark) defined from the register data for year 2019:

- Population density (# people/km^2)
- Mean income (DKK/year)
- Median wealth (DKK/year)
- % unemployment
- % primary or lower education
- SES 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)

Ethnicity was defined by country of origin (Denmark; Western countries (All 28 EU countries and Andorra, Iceland, Liechtenstein, Monaco, Norway, San Marino, Switzerland, Vatican State, Canada, USA, Australia, and New Zealand); non-Western (all others).

Co-morbidities (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-CPH 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.

Table 1. Definition and prevalence of co-morbidities among the 192,041 participants of the AIRCODEN-CPH cohort at the study baseline on March 1, 2020.

	ICD-10 codes	ICD-8 codes	Prevalence, n (%)
Cardiovascular Disease	**I00-99**	**400–459**	**61,607 (32.1%)**
Myocardial Infarction	I21	410	7,197 (3.7%)
Heart Failure	I50	427	4,894 (2.5%)
Atrial fibrillation	I48	427.4, 427.9	9,591 (5.0%)
Stroke (ischemic included)	I61-64	431, 432, 433, 434, 436	8,562 (4.5%)
Respiratory Disease	**J00–J99**	**460–519**	**50,830 (26.5%)**
Asthma	J45-46	493	7,485 (3.9%)
COPD	J40-44	490-492	7,272 (3.8%)
ALRI	J12-18, J20-22	480-486, 466	18,489 (9.6%)
Pneumonia	J12-18	480-486	17,379 (9.0%)
Influenza	J09-11	487-488	1,761 (0.9%)
Lung cancer	**C34**	**162.2–162.9**	**837 (0.4%)**
Diabetes	**E10-14, H36, O24 (excluded O24.4)**	**249, 250**	**9,315 (4.9%)**
Dementia	**F00-03, G30, G31.8-9**	**290.09-11,290.19; 293.09-11,293.19**	**1,821 (0.9%)**

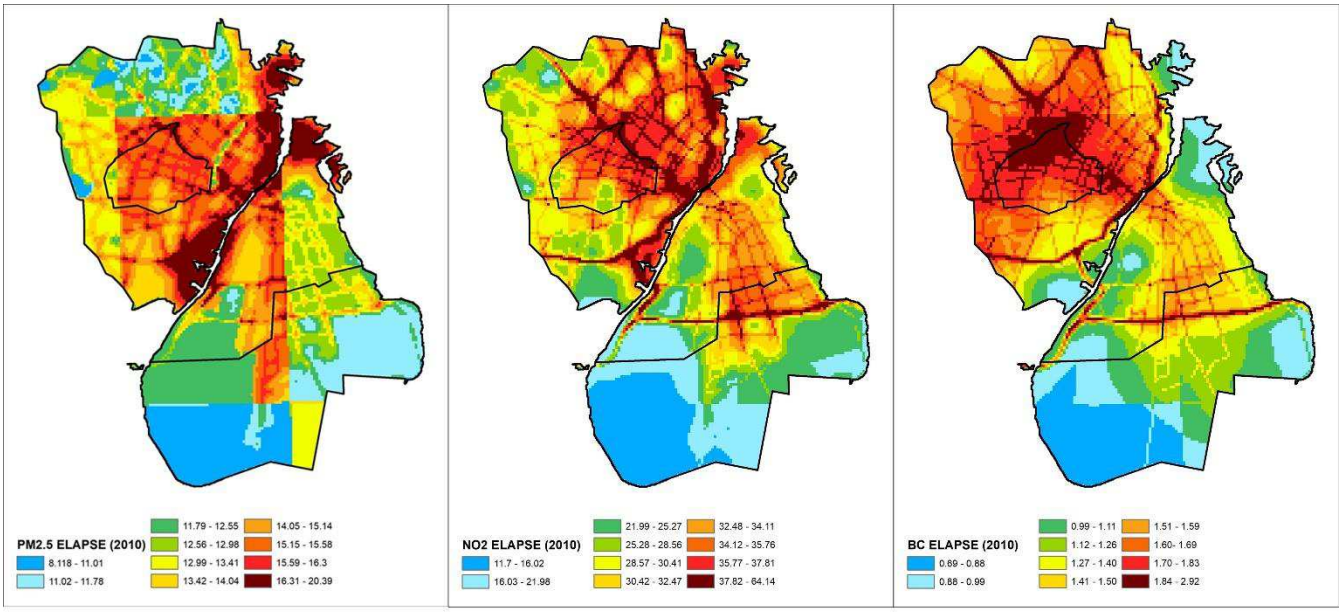
ICD-8/10: International Classification of Diseases 8th/10th version. ICD-8 was used before and ICD-10 after January 1, 1994 (ICD-9 was never implemented in Denmark). COPD=chronic obstructive pulmonary disease. ALRI=acute lower respiratory infection.

Air Pollution Exposure

We used the European-wide hybrid 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 year 2010 at a 100x100m 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 (So et al. 2022). In brief, the LUR model utilized routine monitoring data from the European Environment Agency (EEA) AirBase for $PM_{2·5}$ and NO_2, and 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 pollutants 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). Levels of air pollution for Copenhagen modeled by ELAPSE model in 2010 can be seen in Figure 1.

Figure 1. Mean levels of $PM_{2.5}$, NO_2, and BC in 2010 in Copenhagen estimated by ELAPSE models ($PM_{2.5}$=particulate matter with diameter $\leqslant$ 2.5 μm; NO_2=nitrogen dioxide; BC= black carbon).



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 underlying time scale 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 reason, 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: adjusted for the calendar time (time axis), age (natural spline with 4 degree of freedom), and sex (male, female); Model 2: 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), family income (tertile), household size (one, two, three, four, five and above persons living in household); and Model 3(main model): additionally adjusted for population-level SES including parish-level mean income, and unemployment rate

We fitted single pollutant models for annual mean exposure in 2010 annual mean of $PM_{2.5}$, NO_2, and BC, and O3 estimated by ELAPSE model. To evaluate the shape of the associations for each pollutant, we have estimated exposure-response functions (ERFs) by applying natural cubic splines with three degrees of freedom. In order 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. Effect modification of an association of $PM_{2.5}$ and NO_2 with COVID-19 incidence, and hospitalizationby sex, age, individual-level SES, ethnicity and co-morbidities with cardiovascular disease (CVD), respiratory disease (RD), acute lower respiratory infections (ALRIs), diabetes, lung cancer, dementia, and diabetes, were evaluated by entering interaction terms into the model, and tested by Wald test.

Only subjects with complete information for Model 3 variables were included in the analyses. We presented hazard ratios (HRs) and 95% confidence intervals (CIs) per interquartile range (IQR) increase in pollutant. Besides, we also presented results as per fixed interval increase in each pollutant, which is 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 $\mu g/m^3$ for BC, and 10 $\mu g/m^3$ for O_3. We conducted analyses using R statistical software (version 4.1.2).

The study was approved by the Danish Data Protection Agency.

RESULTS

Of the 192,041 AIRCODEN participants who were 50 years or older and resided in Denmark on March 1, 2020, (and at least one year prior), we excluded 8,397 subjects with missing data on air pollution exposure, 676 with missing data on individual SES information, and 12,127 subjects with missing parish-level SES information. 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 192,041 subjects for final analyses.

During 14 months follow-up covering two pandemic waves (Figure 2), 10,324 individuals tested positive for SARS-CoV-2, 1,563 were hospitalized and 461 died from COVID-19. Compared to 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). Similar patterns but with less pronounced differences were observed with incident COVID-19 cases. COVDI-19 pandemic in Copenhagen was comparable to that for entire Denmark (Figure 3).

Mean levels of $PM_{2.5}$, NO_2 and BC in 2019 were 14.1, 32.3 and 1.5 $\mu g/m^3$, respectively, and were slightly higher in COVID-19 cases than in the total population (Table 2). Strongest positive correlation was observed between NO_2 and BC (0.99) and NO_2 and $PM_{2·5}$ (0.89), and negative between NO_2 and O_3 (-0.99) (Figure 4).

We detected statistically significant positive associations of $PM_{2.5}$, NO_2 and BC with COVID-19 incidence (Table 3), with HR of 1.07 (1.00-1.13) per 5 $\mu g/m^3$ increase in $PM_{2.5}$, 1.03 (1.00-1.06) per 10 $\mu g/m^3$ increase in NO_2, and 1.06 (1.03-1.09) per 0.5 $\mu g/m^3$ increase in BC (Table A1). We also detected assocaitions of $PM_{2.5}$ and BC with COVID-19 hospitalizations that were strongere than those with incidence, with HRs of 1.22 (1.04-1.43) per 5 $\mu g/m^3$ increase in $PM_{2.5}$ and 1.08 (0.99-1.18) per 0.5 $\mu g/m^3$ increase in BC (Table A1). We found positive but not statistically significant (few cases) associations of $PM_{2.5}$ with COVID-19 mortality with HR of , with HRs of 1.18 (0.88-1.59) per 5 $\mu g/m^3$ increase in $PM_{2.5}$ (Table A1), and none with NO_2 or BC. We found no associations of O_3 with any of COVID-19 outcomes. Results were similar when limiting population to Copenhagen

municipality only (Table A2). We also detected associations with all-cause mortality with HR of , with HRs of 1.09 (1.00-1.19) per 5 μg/m^3 increase in $PM_{2.5}$, but none with NO_2 or BC.

ERFs were linear or curvilinear for the majority of the pollutants and COVID-19 outcomes (Figure 5), indicating stronger associations at lower exposure ranges.

We found strongest associations of NO_2 with COVID-19 incidence in the elderly (those 65 years old or older), and of all pollutants in those living in large households with 5 inhabitants or more (Table 4). We found no difference in associations between men and women. When considering co-morbidites at the study baseline, we found strongest associations with both $PM_{2.5}$ and NO_2 in those with prior CVD, which was most pronounced for stroke, but also apparent for heart failure (HF) and atrial fibrillation (AF) (Figure 6). We also detected stronger associations in those with prior RD, although less pronunced for asthma, and for diabetes.Results were similar for COVID-19 hospitalizations (Table A3 and Figure A1).

Figure 2. The COVID-19 pandemic in Copenhagen, Frederiksberg and Tarnby Municipalities between March 1, 2020 and April 26, 2021: daily numbers of COVID-19 positive cases in each municipality.

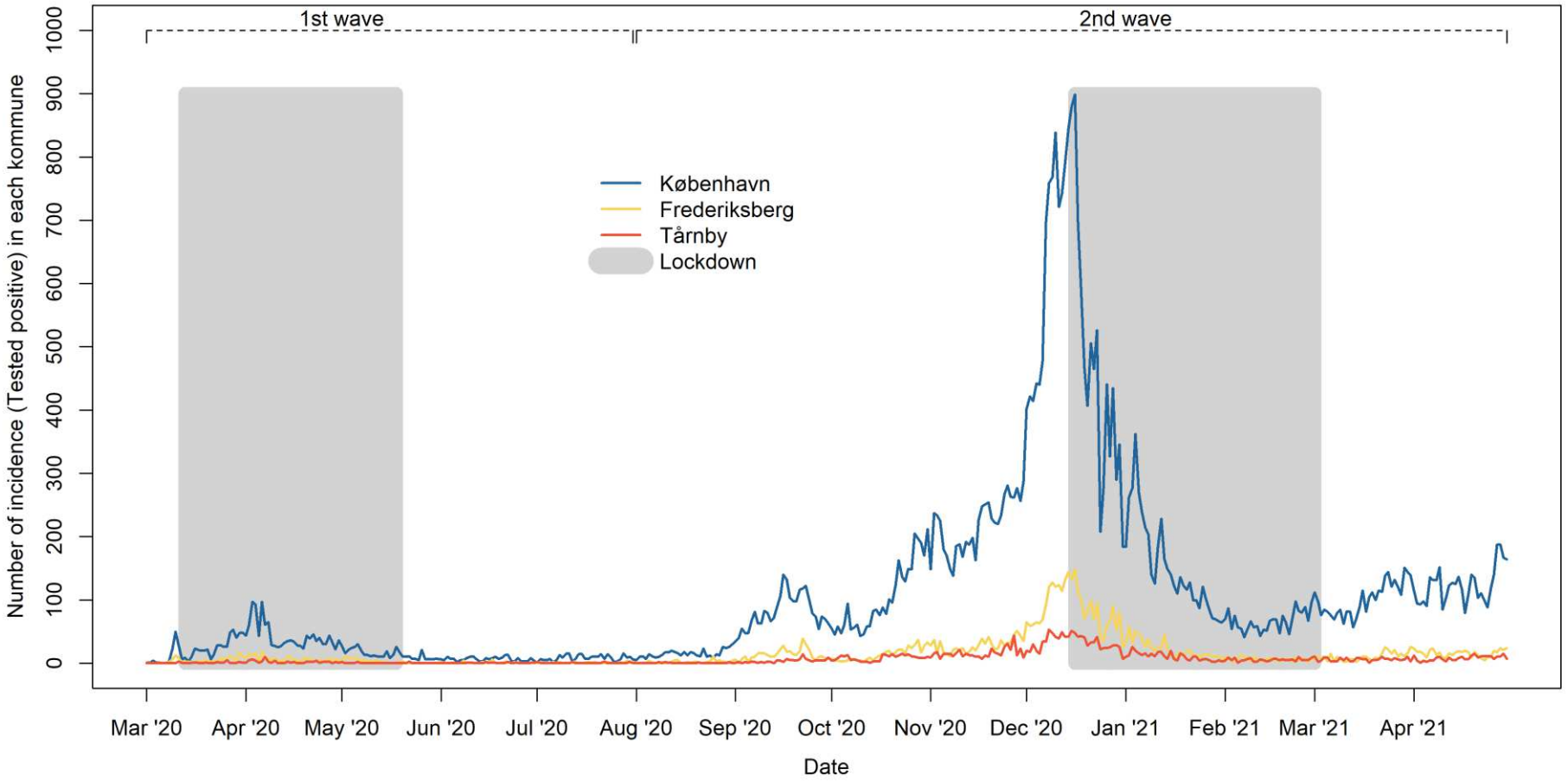


Figure 3. The COVID-19 pandemic in Denmark between March 1, 2020 and April 26, 2021: daily numbers of COVID-19 positive cases, hospital admissions, and deaths in Denmark.

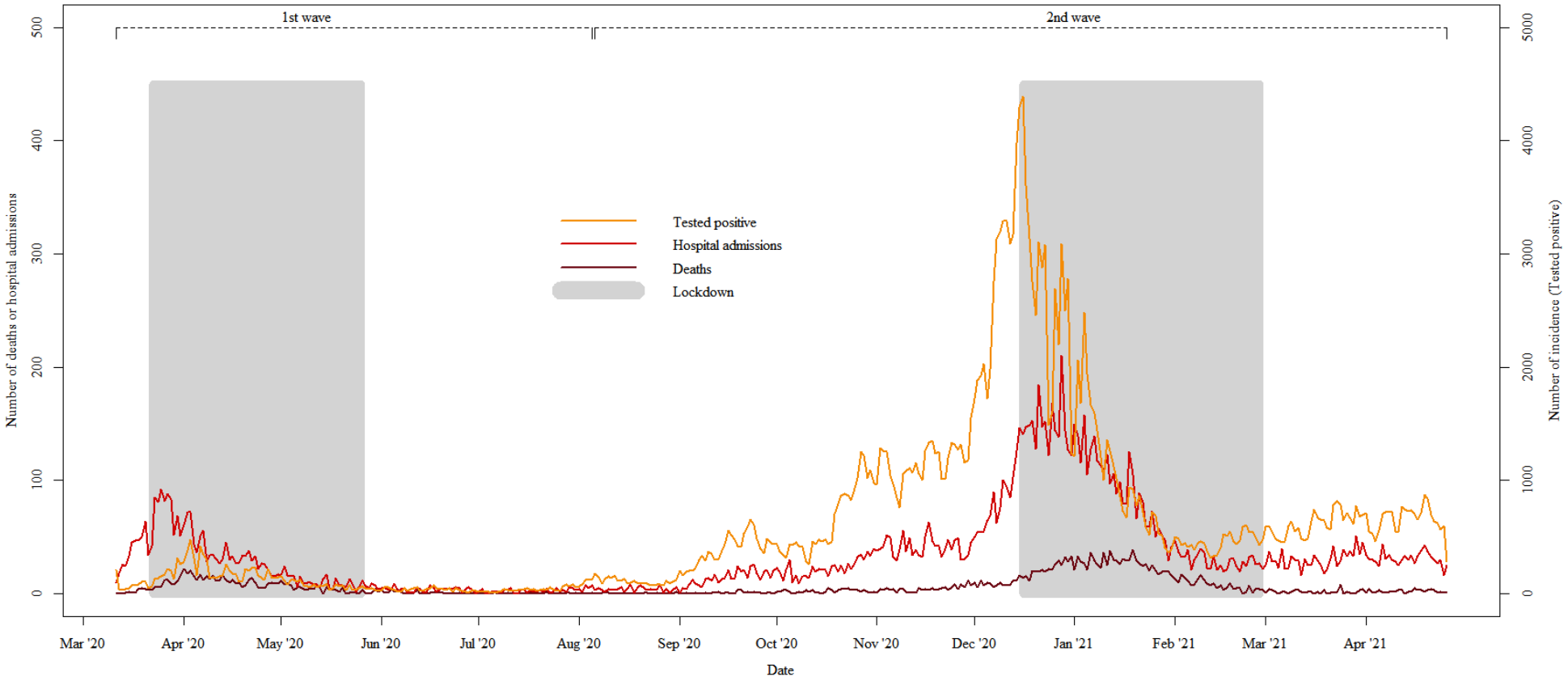


Table 2. Characteristics among the 192,041 participants of the AIRCODEN-CPH cohort at the study baseline on March 1, 2020.

	Total Population	COVID-19 incidence	COVID-19 hospitalization	COVID-19 mortality
N	192,041	10,324	1,563	461
Person-day at risk	/	78,232,794	79,508,681	79,726,090
Follow-up time, day	/	407	414	415
Individual level				
Male, n (%)	90,182 (47.0)	4,920 (47.7)	851 (54.4)	231 (50.1)
Female, n (%)	101,859 (53.0)	5,404 (52.3)	712 (45.6)	230 (49.9)
Age, mean (SD)	65.3 (10.6)	64 (11.4)	73.2 (11.7)	81.2 (10.3)
Married/Partner, n (%)	86,586 (45.1)	5,418 (52.5)	644 (41.2)	118 (25.6)
Income				
Low, n (%)	65,989 (34.4)	3,487 (33.8)	830 (53.1)	270 (58.6)
Middle, n (%)	52,900 (27.5)	2,974 (28.8)	420 (26.9)	141 (30.6)
High, n (%)	73,152 (38.1)	3,863 (37.4)	313 (20.0)	50 (10.8)
Education				
Missing, n (%)	3,976 (2.1)	279 (2.7)	65 (4.2)	23 (5.0)
Primary, n (%)	43,030 (22.4)	2,438 (23.6)	546 (34.9)	189 (41.0)
Upper secondary, n (%)	12,936 (6.7)	726 (7.0)	89 (5.7)	18 (3.9)
Vocational , n (%)	58,007 (30.2)	3,207 (31.1)	497 (31.8)	148 (32.1)
Vocational Bachelor, n (%)	42,009 (21.9)	2,262 (21.9)	248 (15.9)	62 (13.4)
College+, n (%)	32,083 (16.7)	1,412 (13.7)	118 (7.5)	21 (4.6)
Household population				
1-2, n (%)	154,942 (80.7)	7,198 (69.7)	1,314 (84.1)	433 (93.9)
3-4, n (%)	31,053 (16.2)	2,411 (23.4)	171 (10.9)	17 (3.7)
5+, n (%)	6,046 (3.1)	715 (6.9)	78 (5.0)	11 (2.4)
Comorbidity				

Cardiovascular Disease, n (%)	61,607 (32.1)	3,541 (34.3)	895 (57.3)	298 (64.6)
Myocardial Infarction, n (%)	7,197 (3.7)	457 (4.4)	161 (10.3)	57 (12.4)
Heart Failure, n (%)	4,894 (2.5)	300 (2.9)	137 (8.8)	47 (10.2)
Atrial fibrillation, n (%)	9,591 (5.0)	568 (5.5)	190 (12.2)	79 (17.1)
Stroke (ischemic included), n (%)	8,562 (4.5)	508 (4.9)	170 (10.9)	74 (16.1)
Respiratory Disease, n (%)	50,830 (26.5)	3,260 (31.6)	681 (43.6)	207 (44.9)
Asthma, n (%)	7,485 (3.9)	521 (5.0)	93 (6.0)	20 (4.3)
COPD, n (%)	7,272 (3.8)	371 (3.6)	141 (9.0)	58 (12.6)
ALRI, n (%)	18,489 (9.6)	1,235 (12.0)	362 (23.2)	132 (28.6)
Pneumonia, n (%)	17,379 (9.0)	1,150 (11.1)	349 (22.3)	131 (28.4)
Influenza, n (%)	1,761 (0.9)	170 (1.6)	33 (2.1)	6 (1.3)
Lung cancer, n (%)	837 (0.4)	45 (0.4)	15 (1.0)	8 (1.7)
Diabetes, n (%)	9,315 (4.9)	696 (6.7)	231 (14.8)	65 (14.1)
Dementia, n (%)	1,821 (0.9)	224 (2.2)	54 (3.5)	56 (12.1)
Area level				
Mean income, (mean ± SD)	290,626 (55,999)	282,985 (56,781)	278,942 (54,715)	283,073 (51,633)
Unemployment rate % (mean ± SD)	1.4 (0.4)	1.5 (0.4)	1.5 (0.4)	1.5 (0.4)
Air pollution in 2010				
$PM_{2.5}$,$\mu g/m^3$ (mean ± SD)	14.1 (1.6)	14.1 (1.6)	14.2 (1.6)	14.3 (1.6)
NO_2 ,$\mu g/m^3$ (mean ± SD)	32.3 (6.4)	32.4 (6.1)	32.8 (5.7)	32.8 (5.4)
BC ,$\mu g/m^3$ (mean ± SD)	1.5 (0.3)	1.5 (0.3)	1.6 (0.3)	1.6 (0.3)
O_3 ,$\mu g/m^3$ (mean ± SD)	74.2 (5.5)	74.3 (5.8)	74 (5.6)	74.3 (5.9)

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 192,041 participants of the AIRCODEN-CPH cohort.

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
COVID-19 Incidence* (N= 10,324)			
PM_{25}	0.99 (0.96, 1.02)	1.00 (0.97, 1.04)	**1.04 (1.00, 1.07)**
NO_2	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)	**1.02 (1.00, 1.04)**
BC	**1.05 (1.02, 1.07)**	**1.05 (1.03, 1.08)**	**1.04 (1.02, 1.07)**
O_3	1.01 (0.98, 1.05)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
COVID-19 Hospitalization* (N= 1,563)			
PM_{25}	1.07 (0.98, 1.16)	1.06 (0.97, 1.15)	**1.11 (1.02, 1.21)**
NO_2	**1.06 (1.00, 1.11)**	1.03 (0.98, 1.09)	1.03 (0.98, 1.08)
BC	**1.10 (1.03, 1.16)**	**1.07 (1.01, 1.14)**	**1.06 (1.00, 1.12)**
O_3	0.93 (0.85, 1.01)	0.96 (0.88, 1.05)	0.96 (0.87, 1.05)
COVID-19 Mortality (N= 461)			
PM_{25}	1.09 (0.94, 1.27)	1.08 (0.92, 1.25)	1.09 (0.93, 1.28)
NO_2	1.01 (0.92, 1.11)	0.97 (0.88, 1.06)	0.97 (0.88, 1.06)
BC	1.06 (0.95, 1.18)	1.02 (0.91, 1.14)	1.01 (0.90, 1.13)
O_3	0.98 (0.83, 1.15)	1.03 (0.87, 1.22)	1.04 (0.87, 1.23)
All-cause Mortality (N= 5,098)			
PM_{25}	1.04 (0.99, 1.08)	1.01 (0.96, 1.06)	**1.05 (1.00, 1.10)**
NO_2	**1.04 (1.01, 1.07)**	1.00 (0.97, 1.03)	1.00 (0.97, 1.03)
BC	**1.04 (1.01, 1.08)**	1.00 (0.97, 1.03)	1.00 (0.96, 1.03)
O_3	0.93 (0.88, 0.98)	0.99 (0.94, 1.04)	0.98 (0.93, 1.03)

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: 2.67 $\mu g/m^3$ for $PM_{2.5}$, 6.25 $\mu g/m^3$ for NO_2, 0.35 $\mu g/m^3$ for BC, 10.16 $\mu g/m^3$ for O_3.
Model 1 adjusted for calendar time (time axis), sex (male, female), and age at baseline (natural spline with four degrees of freedom); Model 2 additionally adjusted for civil status, household size, family income, and education; Model 3 further adjusted for parish-level mean income, unemployment rate.

Figure 4: Pearson correlation coefficients between air pollutants estimated by the ELAPSE model in 2010 among the 192,041 participants of the AIRCODEN-CPH cohort (BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 μm).

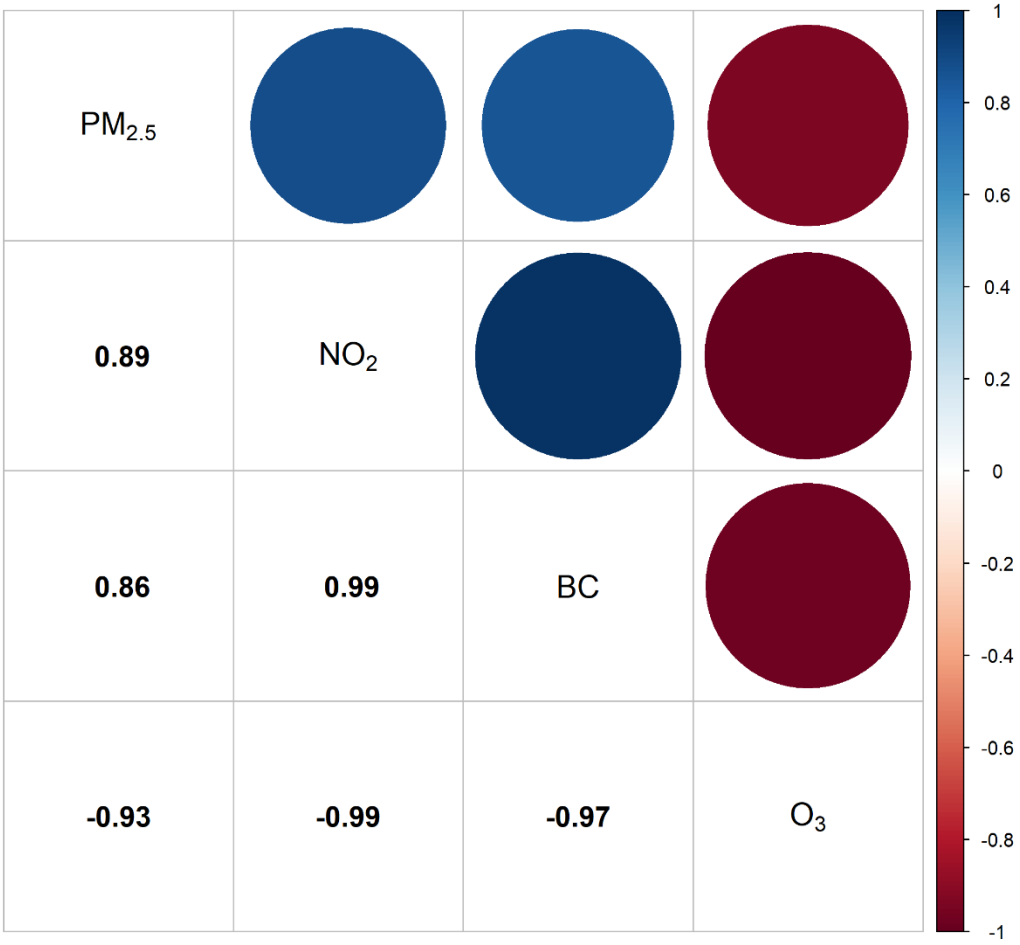
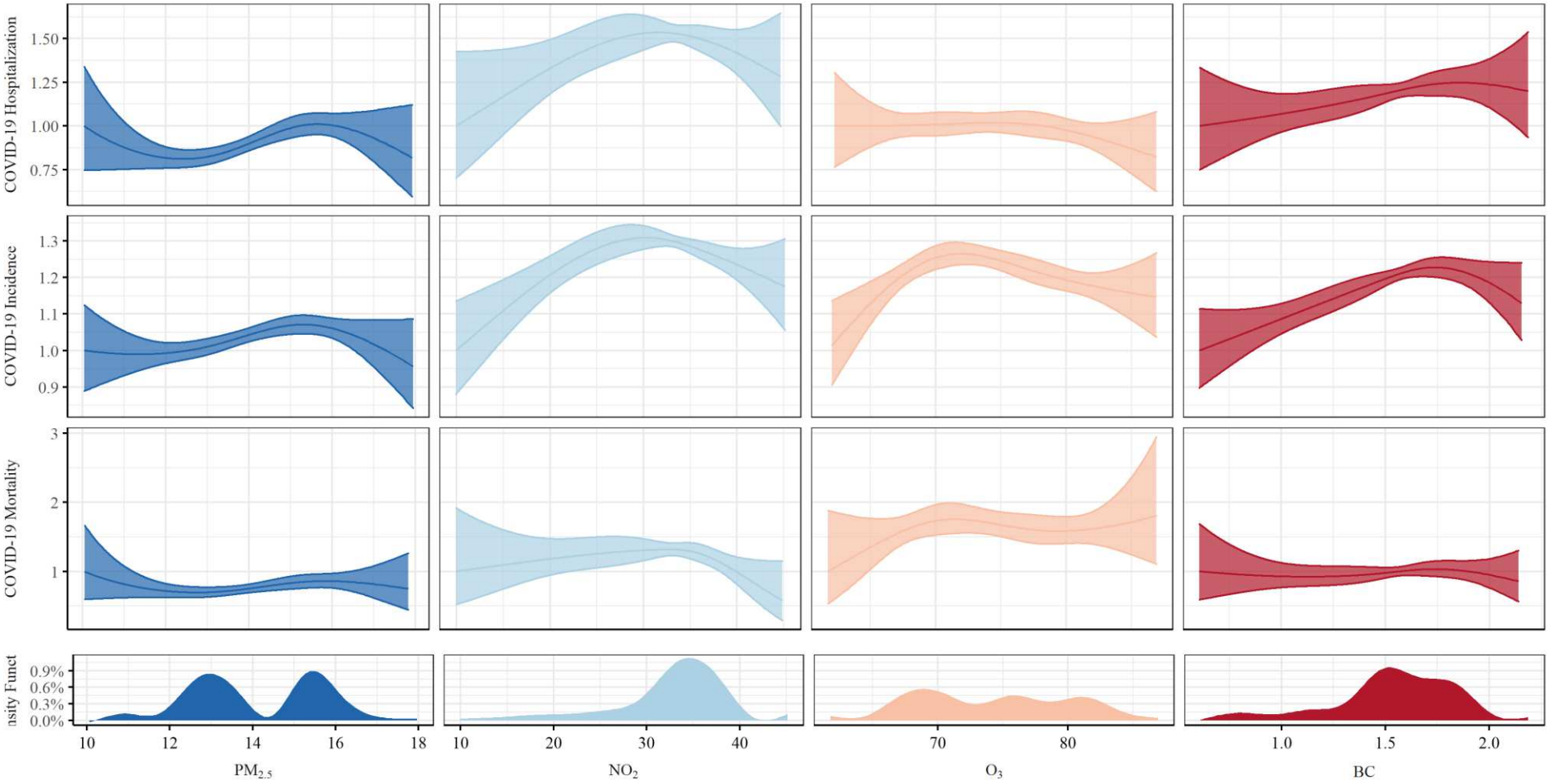


Figure 5. The shape of the associations between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 192,041participants of the AIRCODEN-CPH cohort.



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. Model adjusted for calendar time (time axis), sex (male, female) , and age at baseline (natural spline with four degrees of freedom); individual covariates (civil status, household size, family income, and education); and area-level covariates (parish-level mean income, unemployment rate.

Table 4. Effect modification of the association between long-term exposure to air pollution and COVID-19 incidence among the 192,041 participants of the AIRCODEN-CPH cohort by sex, age, and individual-level SES characteristic at the cohort baseline on March 1, 2020.

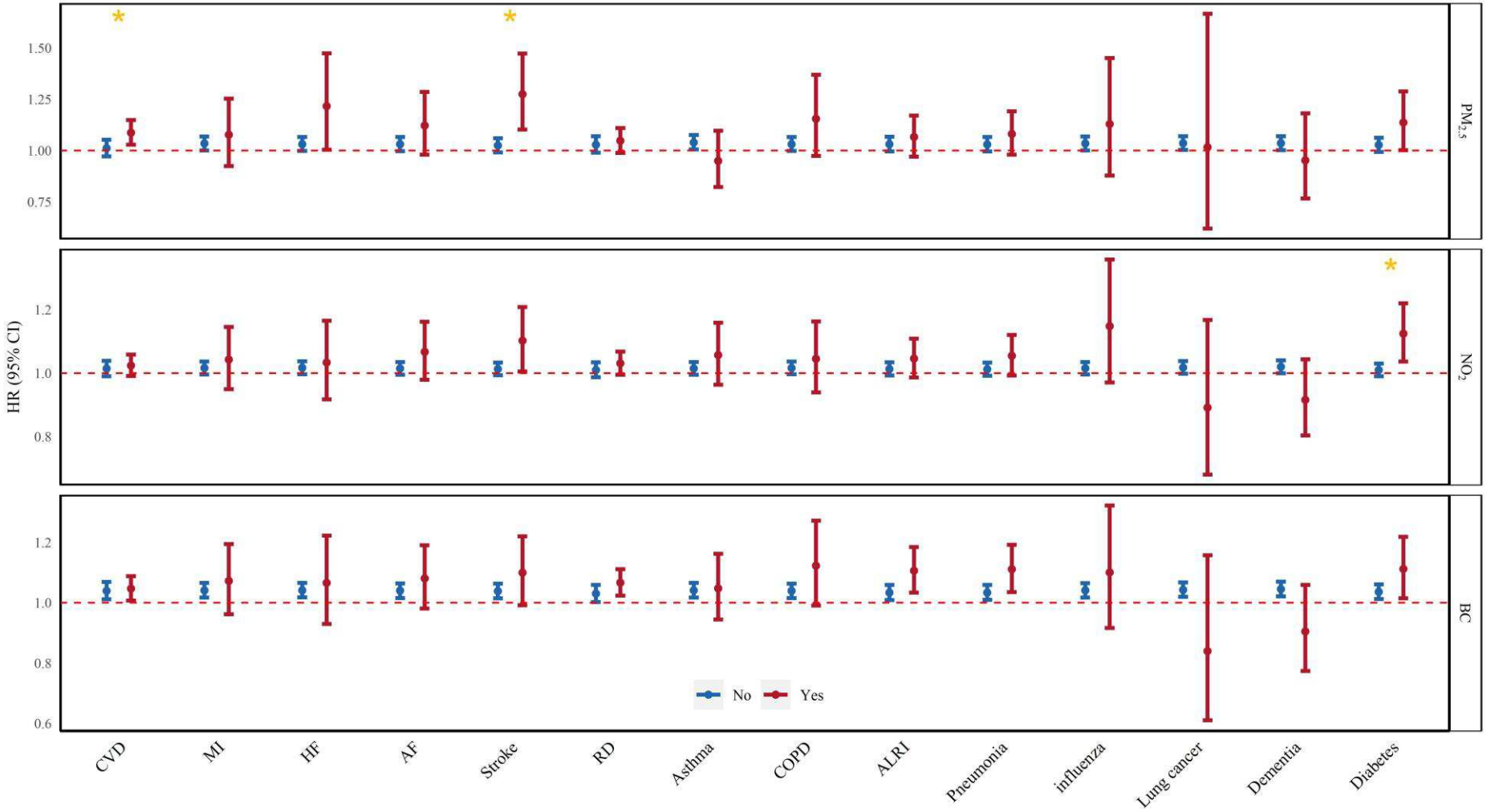
	PM2.5	NO2	BC	Global p-value
	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age				
Less than 65	1.01 (0.97, 1.05)	1.01 (0.99, 1.04)	1.04 (1.01, 1.07)	$PM_{2.5}$: 0.04; NO_2: 0.72; BC: 0.73
65+	1.08 (1.03, 1.14)	1.02 (0.99, 1.06)	1.05 (1.01, 1.09)	
Sex				
Male	1.04 (0.99, 1.09)	1.03 (1.00, 1.06)	1.05 (1.01, 1.08)	$PM_{2.5}$: 0.85; NO_2: 0.21; BC: 0.73
Female	1.03 (0.99, 1.08)	1.01 (0.98, 1.03)	1.04 (1.01, 1.07)	
Country of Origin				
Denmark	1.04 (1.00, 1.08)	1.00 (0.98, 1.03)	1.02 (0.99, 1.05)	
Western countries	1.01 (0.86, 1.20)	0.99 (0.89, 1.11)	1.08 (0.95, 1.23)	$PM_{2.5}$: 0.10; NO_2: 0.94; BC: 0.07
Other countries	1.03 (0.96, 1.10)	1.06 (1.01, 1.11)	1.09 (1.03, 1.15)	
Married Status				
Unmarried	0.97 (0.89, 1.05)	1.00 (0.95, 1.06)	1.05 (0.98, 1.12)	
Divorced	1.04 (0.97, 1.11)	1.01 (0.97, 1.05)	1.03 (0.98, 1.08)	$PM_{2.5}$: 0.32; NO_2: 0.60; BC: 0.88
Widowed	1.08 (0.98, 1.19)	0.99 (0.93, 1.05)	1.07 (0.99, 1.14)	
Married	1.05 (1.00, 1.09)	1.03 (1.00, 1.06)	1.04 (1.01, 1.08)	
Income				

Low	1.02 (0.97, 1.08)	1.03 (0.99, 1.07)	1.06 (1.02, 1.11)	
Middle	1.04 (0.98, 1.10)	1.00 (0.96, 1.04)	1.04 (0.99, 1.08)	$PM_{2.5}$: 0.90; NO_2: 0.49; BC: 0.52
High	1.04 (0.99, 1.10)	1.02 (0.99, 1.05)	1.03 (0.99, 1.07)	
Education				
Missing	1.10 (0.91, 1.34)	1.05 (0.93, 1.17)	1.11 (0.97, 1.28)	
Primary	1.03 (0.96, 1.10)	1.02 (0.98, 1.06)	1.06 (1.01, 1.12)	
Upper secondary	0.93 (0.83, 1.05)	1.02 (0.95, 1.10)	1.06 (0.98, 1.16)	$PM_{2.5}$: 0.04; NO_2: 1.00; BC: 0.76
Vocational	0.99 (0.93, 1.05)	1.02 (0.98, 1.06)	1.04 (1.00, 1.08)	
Vocational Bachelor	1.08 (1.01, 1.16)	1.01 (0.97, 1.05)	1.03 (0.98, 1.08)	
College+	1.12 (1.03, 1.22)	1.02 (0.97, 1.07)	1.02 (0.96, 1.08)	
Household population				
1-2	1.04 (1.00, 1.08)	1.01 (0.99, 1.03)	1.04 (1.01, 1.07)	
3-4	0.99 (0.92, 1.05)	1.02 (0.98, 1.06)	1.03 (0.98, 1.08)	$PM_{2.5}$: 0.10; NO_2: 0.13; BC: 0.29
5+	1.14 (1.01, 1.28)	1.10 (1.02, 1.18)	1.11 (1.02, 1.22)	

HR=hazard ratio. CI=confidence interval. NO_2=nitrogen dioxide. $PM_{2.5}$=particulate matter with diameter $\leq$ 2.5 μm. Results are presented for interquartile range increase: 2.67 $\mu g/m^3$ for $PM_{2.5}$, 6.25 $\mu g/m^3$ for NO_2, and 0.35 $\mu g/m^3$ for BC.

*Wald test was used to calculate the global P-value.

Figure 6. Effect modification of the association between long-term exposure to air pollution and COVID-19 incidence among the 192,041 participants of the AIRCODEN-CPH cohort by co-morbidities 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. Results are presented for interquartile range increase: 2.67 μg/m^3 for $PM_{2.5}$, 6.25 μg/m^3 for NO_2, and 0.35 μg/m^3 for BC. *Wald test was used to calculate the global P-value, and results with P-value <0.05 are highlighted with a star.

DISCUSSION

In this large study in greater Copenhagenresidents 50 years old and older, we detected positive associations between long-term exposure to $PM_{2.5}$, NO_2, and BC and risk of getting infected with SARS-CoV-2, as well as getting hospitalized or dying from COVID-19. We find that elderly (aged 65 years or older), individuals with major chronic cardiovascular and respiratory diseases, and diabetes, as well as those living in households with more than five people, were most vulnerable to the harmful effects of air pollution.

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, 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 et al. who in 62,848 residents of Varese (of whom 4,408 tested positive for COVID-19 in the 1st year of pandemic) detected 5.1% and 2% increase in COVID-19 rate for each unit ($\mu g/m^3$) increase in $PM_{2.5}$ and NO2, respectively (Veronesi et al. 2022). Sheridan et al. has in 424,721 subjects from UK Biobank (of whom tested 10,790 positive between March 16 and December 31, 2020) detected OR of 1.06 and 1.05 for COVID-19 incidence for each 1.3 and 9.9 $\mu g/m^3$ 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). Nobile et al. has 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), 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 $\mu g/m^3$ increase in $PM_{2.5}$ and NO_2, respectively (Nobile et al. 2022) Furthermore, our results agree with those of Kogevinas et al. 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 with increasing severity of COVID-19 outcomes was also observed by Kogevinas et al.(Kogevinas et al. 2021) and Nobile et al.(Nobile et al. 2022) but not in Sheridan et al. (Sheridan et al. 2022).

We have found indication of curvilinear shape of assocaition, in line with large studies based on low-exposure to air pollution from Europe and Canada (Brauer et al. 2019; Stafoggia et al. 2022b; Strak et al. 2021), and recent meta-analyses on studies of air-pollution and mortality (Chen and Hoek 2020), suggesting stronger association in lower level exposure. Within ELAPSE project, with this same exposure as used here, we have earlier documented associations of $PM_{2.5}$ with all-cause mortality in Europe in studies including Danish data (Stafoggia et al. 2022a; Strak et al. 2021) and in Denmark in a recent nationwide study using ELAPSE data (So et al. 2022) in line with those reported here (Table 4), and also indicating curvi-linear ERF, supporting the plausibility of our findings.

We have detcted associations with PM2.5, NO_2 and BC, most consistent and strongest for all three outcomes with $PM_{2.5}$. This is in line with Sheridan et al. and Varonesi et al. 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 report novel association with traffic-related pollutant BC and COVID-19, as the first study to date. Our finding of null associations with O_3, are in line with Veronesi et al. 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. 2022a; 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 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 elderly and chronic disease patients. Veronesi et al. is the only study that have 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. Varonesi et al. did notably find indication of stronger associations of $PM_{2.5}$ with COVID-19 incidence in coronary heart disease (CHD) and obstructive lung disease patients, in line with our findings (Veronesi et al. 2022). Increased susceptibility of patients to harms of air pollution, with major chronic diseases which have been earlier linked to air pollution, makes biological sense,

Biological plausibility

Although exact molecular mechanisms by which PM and gaseous pollutant exposure 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). Exposure to air pollution may promote viral entry, replication and assembly, activate proinflammatory transcription factors, producing local inflammation. Furthermore, pollutant exposure reduces mucociliary clearance, promotes epithelial permeability, prevents macrophage uptake, and disrupts natural killer cell function, all of which can increase viral spread and inflammation(Woodby et al. 2021). Subsequent enhanced inflammation can trigger neutrophil recruitment and further amplify inflammatory processes. Moreover, since pollution is believed to skew adaptive immune responses toward allergic/bacterial responses instead of antiviral immune responses, exposure to air pollution may result in enhanced virus-induced tissue damage and inflammation, promoting dysfunction of a variety of organs, including the lungs, heart, kidney, and brain, resulting in death (Woodby et al. 2021). Apart from this direct impact of air pollution on immune responses, air pollution likely increases risk of COVID-19 severity and death indirectly by increasing risk of related co-morbidities (respiratory, cardiovascular and metabolic diseases) which increase 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.

Strengths

Our study is one of the largest to date, facilitated by the internationally unique access to high-quality individual-level Danish COVID-19 surveillance data for entire population of

Copenhagen. Furthermore, as Denmark had one of the most intense testing strategies, and where testing was offered free of charge, we have 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 in the first 14 months of the pandemic, many several times per month. Secondly, we benefited from detailed data on disease history allowing us to study effect modification by co-morbidities, and 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.

Limitations

Our study has several limitations. We lack data on individual-level lifestyle factors, such as smoking, physical activity, BMI, diet, etc. which may be relevant confounders. We also lack data on residence in nursing homes, and could not make sensitivity analyses excluding nursing home residents. Notably, Denmark has generally managed COVID-19 pandemic well, without any excess mortality, and without large COVID-19 mortality clusters in nursing homes as seen in Italy and other locations. Furthermore, our COVID-19 surveillance system, especially in the early stages of the pandemic, could only identify a selected sample of all infected individuals, those with severe symptoms, close contacts of primary cases with symptoms, those who were hospitalized for other causes, etc. The testing policy was massively expanded in the second wave, where testing free of charge was offered to all, and when large portion of populations was tested daily, as negative test was required to enter workplaces, universities, schools, restaurants, movie theaters, public transport, etc. Therefore, our definition of SARS-CoV-2 incidence is only partial, especially in the first wave.

We lacked data on vaccinations, and could not address whether vaccination would have affected observed associations. First vaccination in Denmark was given on December 27th, 2020, and only a fraction of population was vaccinated by April 26th, 2021, 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.

CONCLUSION

In a large Copenhagen-wide study covering first 14 months of COVID-19 pandemic, we have found that long-term exposure to air pollution at very low levels, those 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. Chronic cardiometabolic, respiratory and diabetes patients, elderly, are most susceptible and most likely to contract SARS-CoV-2 or develop COVID-19 due to 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 in the heart of the current and future pandemic mitigation strategies, as it would provide more resilient populations to SARS-CoV-2 and alike infections. In addition, reduction of air pollution would prevent substantial cases of new major chronic diseases improve quality of life and prognosis of chronic disease patients, and, by reducing fossil fuel emission, help mitigate the global climate change crisis.

IMPLICATIONS OF THE FINDINGS

This large study provide strong new evidence in support of causal association between 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 (seasonal influenza and pneumonias, etc.). Reductions in air pollution would also bring other major health benefits, in terms of prevention of major chronic non-communicable diseases and providing for better quality of life and better disease prognosis for chronic disease patients, as well as in mitigating impact of climate change on health.

REFERENCES

Atkins JL, Masoli JAH, Delgado J, Pilling LC, Kuo CL, Kuchel GA, et al. 2020. Preexisting Comorbidities Predicting COVID-19 and Mortality in the UK Biobank Community Cohort. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 75:2224–2230; doi:10.1093/gerona/glaa183.

Baadsgaard M, Quitzau J. 2011. Danish registers on personal income and transfer payments. Scand J Public Health 39:103–105; doi:10.1177/1403494811405098.

Bowe B, Xie Y, Gibson AK, Cai M, van Donkelaar A, Martin R v., et al. 2021. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: Cohort study. Environ Int 154; doi:10.1016/j.envint.2021.106564.

Bowe B, Xie Y, Yan Y, Al-Aly Z. 2019. Burden of Cause-Specific Mortality Associated With PM2.5 Air Pollution in the United States. JAMA Netw Open 2:e1915834; doi:10.1001/jamanetworkopen.2019.15834.

Bozack A, Pierre S, DeFelice N, Colicino E, Jack D, Chillrud SN, et al. 2022. Long-Term Air Pollution Exposure and COVID-19 Mortality: A Patient-Level Analysis from New York City. Am J Respir Crit Care Med 205:651–662; doi:10.1164/RCCM.202104-0845OC.

Brandt J, Christensen JH, Frohn LM, Berkowicz R, Brandt J, Christensen JH, et al. 2003. Air pollution forecasting from regional to urban street scale implementation and validation for two cities in Denmark. PCE 28:335–344; doi:10.1016/S1474-7065(03)00054-8.

Brandt J, Silver JD, Frohn LM, Geels C, Gross A, Hansen AB, et al. 2012. An integrated model study for Europe and North America using the Danish Eulerian Hemispheric Model with focus on intercontinental transport of air pollution. Atmos Environ 53:156–176; doi:10.1016/J.ATMOSENV.2012.01.011.

Brauer M, Brook JR, Christidis T, Chu Y, Crouse DL, Erickson A, et al. 2019. Mortality-Air Pollution Associations in Low-Exposure Environments (MAPLE): Phase 1. Res Rep Health Eff Inst 1–87.

Carey IM, Anderson HR, Atkinson RW, Beevers S, Cook DG, Dajnak D, et al. 2016. Traffic pollution and the incidence of cardiorespiratory outcomes in an adult cohort in London. Occup Environ Med 73:849–856; doi:10.1136/OEMED-2015-103531.

Carey IM, Atkinson RW, Kent AJ, van Staa T, Cook DG, Anderson HR. 2013. Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. Am J Respir Crit Care Med 187:1226–1233; doi:10.1164/RCCM.201210-1758OC.

Chen C, Wang J, Kwong J, Kim JH, van Donkelaar A, Martin R v., et al. 2022. Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study. CMAJ Canadian Medical Association Journal 194:E693–E700; doi:10.1503/cmaj.220068.

Chen J, Hoek G. 2020. Long-term exposure to PM and all-cause and cause-specific mortality: A systematic review and meta-analysis. Environ Int; doi:10.1016/j.envint.2020.105974.

Cole MA, Ozgen C, Strobl E. 2020. Air Pollution Exposure and Covid-19 in Dutch Municipalities. Environ Resour Econ (Dordr) 76:581; doi:10.1007/S10640-020-00491-4.

Danesh Yazdi M, Wang Y, Di Q, Wei Y, Requia WJ, Shi L, et al. 2021. Long-Term Association of Air Pollution and Hospital Admissions among Medicare Participants Using a Doubly Robust Additive Model. Circulation 143:1584–1596; doi:10.1161/CIRCULATIONAHA.120.050252.

de Hoogh K, Chen J, Gulliver J, Hoffmann B, Hertel O, Ketzel M, et al. 2018. Spatial PM 2.5, NO 2, O 3 and BC models for Western Europe - Evaluation of spatiotemporal stability. Environ Int 120:81–92; doi:10.1016/J.ENVINT.2018.07.036.

de Hoogh K, Gulliver J, Donkelaar A van, Martin R v., Marshall JD, Bechle MJ, et al. 2016. Development of West-European PM 2.5 and NO 2 land use regression models incorporating satellite-derived and chemical transport modelling data. Environ Res 151:1–10; doi:10.1016/J.ENVRES.2016.07.005.

Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. 2017. Air pollution and mortality in the medicare population. New England Journal of Medicine; doi:10.1056/NEJMoa1702747.

Elliott J, Bodinier B, Whitaker M, Delpierre C, Vermeulen R, Tzoulaki I, et al. 2021. COVID-19 mortality in the UK Biobank cohort: revisiting and evaluating risk factors. Eur J Epidemiol 36:299–309; doi:10.1007/S10654-021-00722-Y.

Health Effects Institute. 2020. State of Global Air 2020. Special Report.

Heederik DJJ, Smit LAM, Vermeulen RCH. 2020. Go slow to go fast: A plea for sustained scientific rigour in air pollution research during the COVID-19 pandemic. European Respiratory Journal; doi:10.1183/13993003.01361-2020.

Hvidtfeldt UA, Ketzel M, Sørensen M, Hertel O, Khan J, Brandt J, et al. 2018. Evaluation of the Danish AirGIS air pollution modeling system against measured concentrations of

PM2.5, PM10, and black carbon. Environmental Epidemiology 2:e014; doi:10.1097/EE9.0000000000000014.

Jensen VM, Rasmussen AW. 2011. Danish education registers. Scand J Public Health 39:91–94; doi:10.1177/1403494810394715.

Jerrett M. 2022. Air Pollution as a Risk for Death from Infectious Respiratory Disease. Am J Respir Crit Care Med 205:1374–1375; doi:10.1164/RCCM.202202-0351ED.

Katanoda K, Sobue T, Satoh H, Tajima K, Suzuki T, Nakatsuka H, et al. 2011. An association between long-term exposure to ambient air pollution and mortality from lung cancer and respiratory diseases in Japan. J Epidemiol 21:132–143; doi:10.2188/JEA.JE20100098.

Kazemiparkouhi F, Eum K do, Wang B, Manjourides J, Suh HH. 2020. Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. J Expo Sci Environ Epidemiol 30:650–658; doi:10.1038/S41370-019-0135-4.

Khan J, Kakosimos K, Raaschou-Nielsen O, Brandt J, Jensen SS, Ellermann T, et al. 2019. Development and performance evaluation of new AirGIS – A GIS based air pollution and human exposure modelling system. Atmos Environ 198:102–121; doi:10.1016/J.ATMOSENV.2018.10.036.

Kogevinas M, Castaño-Vinyals G, Karachaliou M, Espinosa A, de Cid R, Garcia-Aymerich J, et al. 2021. Ambient Air Pollution in Relation to SARS-CoV-2 Infection, Antibody Response, and COVID-19 Disease: A Cohort Study in Catalonia, Spain (COVICAT Study). Environ Health Perspect 129; doi:10.1289/EHP9726.

Konstantinoudis G, Padellini T, Bennett J, Davies B, Ezzati M, Blangiardo M. 2021. Long-term exposure to air-pollution and COVID-19 mortality in England: A hierarchical spatial analysis. Environ Int 146; doi:10.1016/J.ENVINT.2020.106316.

Liang D, Shi L, Zhao J, Liu P, Schwartz J, Gao S, et al. 2020. Urban Air Pollution May Enhance COVID-19 Case-Fatality and Mortality Rates in the United States. medRxiv 2020.05.04.20090746; doi:10.1101/2020.05.04.20090746.

Lim CC, Hayes RB, Ahn J, Shao Y, Silverman DT, Jones RR, et al. 2019. Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. Am J Respir Crit Care Med 200:1022–1031; doi:10.1164/RCCM.201806-1161OC.

Lin DY, Ying Z. 1994. Semiparametric Analysis of the Additive Risk Model. Biometrika 81:61; doi:10.2307/2337050.

Liu S, Lim YH, Chen J, Strak M, Wolf K, Weinmayr G, et al. 2022. Long-term Air Pollution Exposure and Pneumonia-related Mortality in a Large Pooled European Cohort. Am J Respir Crit Care Med 205:1429–1439; doi:10.1164/RCCM.202106-1484OC/SUPPL_FILE/DISCLOSURES.PDF.

Mendy A, Wu X, Keller JL, Fassler CS, Apewokin S, Mersha TB, et al. 2021. Air pollution and the pandemic: Long-term PM 2.5 exposure and disease severity in COVID-19 patients. Respirology 26:1181–1187; doi:10.1111/RESP.14140.

Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. 2010. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. Am J Respir Crit Care Med; doi:10.1164/rccm.200901-0160OC.

Nobile F, Michelozzi P, Ancona C, Cappai G, Cesaroni G, Davoli M, et al. 2022. Air pollution, SARS-CoV-2 incidence and COVID-19 mortality in Rome - a longitudinal study. Eur Respir J 60:2200589; doi:10.1183/13993003.00589-2022.

Petersson F, Baadsgaard M, Thygesen LC. 2011. Danish registers on personal labour market affiliation. Scand J Public Health 39:95–98; doi:10.1177/1403494811408483.

Pinault LL, Weichenthal S, Crouse DL, Brauer M, Erickson A, Donkelaar A van, et al. 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ Res 159:406–415; doi:10.1016/J.ENVRES.2017.08.037.

Pope CA, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, et al. 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109:71–77; doi:10.1161/01.CIR.0000108927.80044.7F.

Pope CA, Lefler JS, Ezzati M, Higbee JD, Marshall JD, Kim SY, et al. 2019. Mortality Risk and Fine Particulate Air Pollution in a Large, Representative Cohort of U.S. Adults. Environ Health Perspect 127; doi:10.1289/EHP4438.

Raaschou-Nielsen O, Thorsteinson E, Antonsen S, Holst GJ, Sigsgaard T, Geels C, et al. 2020. Long-term exposure to air pollution and mortality in the Danish population a nationwide study. EClinicalMedicine 28; doi:10.1016/J.ECLINM.2020.100605.

Salimi F, Morgan G, Rolfe M, Samoli E, Cowie CT, Hanigan I, et al. 2018. Long-term exposure to low concentrations of air pollutants and hospitalisation for respiratory diseases: A prospective cohort study in Australia. Environ Int 121:415–420; doi:10.1016/J.ENVINT.2018.08.050.

Schmidt M, Pedersen L, Sørensen HT. 2014. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 29:541–9; doi:10.1007/s10654-014-9930-3.

Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. 2015. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol 7:449–90; doi:10.2147/CLEP.S91125.

Sheridan C, Klompmaker J, Cummins S, James P, Fecht D, Roscoe C. 2022. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: Observational evidence from UK Biobank. Environ Pollut 308; doi:10.1016/J.ENVPOL.2022.119686.

Shin HH, Cakmak S, Brion O, Villeneuve P, Turner MC, Goldberg MS, et al. 2014. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. Environ Res 134:482–487; doi:10.1016/J.ENVRES.2014.05.016.

So R, Andersen ZJ, Chen J, Stafoggia M, de Hoogh K, Katsouyanni K, et al. 2022. Long-term exposure to air pollution and mortality in a Danish nationwide administrative

cohort study: Beyond mortality from cardiopulmonary disease and lung cancer. Environ Int 164; doi:10.1016/J.ENVINT.2022.107241.

Stafoggia M, Oftedal B, Chen J, Rodopoulou S, Renzi M, Atkinson RW, et al. 2022a. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet Health 6:e9–e18; doi:10.1016/S2542-5196(21)00277-1.

Stafoggia M, Oftedal B, Chen J, Rodopoulou S, Renzi M, Atkinson RW, et al. 2022b. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet Health 6:e9–e18; doi:10.1016/S2542-5196(21)00277-1.

Strak M, Weinmayr G, Rodopoulou S, Chen J, de Hoogh K, Andersen ZJ, et al. 2021. Long term exposure to low level air pollution and mortality in eight European cohorts within the ELAPSE project: pooled analysis. BMJ 374; doi:10.1136/BMJ.N1904.

Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. 2021. Links between air pollution and COVID-19 in England. Environ Pollut 268; doi:10.1016/J.ENVPOL.2020.115859.

Turner MC, Jerrett M, Pope CA, Krewski D, Gapstur SM, Diver WR, et al. 2016. Long-Term Ozone Exposure and Mortality in a Large Prospective Study. Am J Respir Crit Care Med 193:1134–1142; doi:10.1164/RCCM.201508-1633OC.

Veronesi G, de Matteis S, Calori G, Pepe N, Ferrario MM. 2022. Long-term exposure to air pollution and COVID-19 incidence: a prospective study of residents in the city of Varese, Northern Italy. Occup Environ Med 79:192–199; doi:10.1136/OEMED-2021-107833.

Villeneuve PJ, Goldberg MS. 2020. Methodological considerations for epidemiological studies of air pollution and the sars and COVID-19 coronavirus outbreaks. Environ Health Perspect 128:095001-1-095001–13; doi:10.1289/EHP7411.

Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. 2020. Factors associated with COVID-19-related death using OpenSAFELY. Nature 584:430–436; doi:10.1038/S41586-020-2521-4.

Woodby B, Arnold MM, Valacchi G. 2021. SARS-CoV-2 infection, COVID-19 pathogenesis, and exposure to air pollution: What is the connection? Ann N Y Acad Sci 1486:15–38; doi:10.1111/NYAS.14512.

Wu X, Nethery RC, Sabath BM, Braun D, Dominici F. 2020. Exposure to air pollution and COVID-19 mortality in the United States: A nationwide cross-sectional study. medRxiv; doi:10.1101/2020.04.05.20054502.

Yang Y, Tang R, Qiu H, Lai PC, Wong P, Thach TQ, et al. 2018. Long term exposure to air pollution and mortality in an elderly cohort in Hong Kong. Environ Int 117:99–106; doi:10.1016/J.ENVINT.2018.04.034.

Yorifuji T, Kashima S, Tsuda T, Ishikawa-Takata K, Ohta T, Tsuruta KI, et al. 2013. Long-term exposure to traffic-related air pollution and the risk of death from hemorrhagic

stroke and lung cancer in Shizuoka, Japan. Sci Total Environ 443:397–402; doi:10.1016/J.SCITOTENV.2012.10.088.

APPENDIX

Table A1: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 192,041 participants of the AIRCODEN-CPH cohort. (per fixed interval increase)

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
COVID-19 Incidence* (N= 10,324)			
PM_{25}	0.97 (0.92, 1.03)	1.01 (0.95, 1.07)	1.07 (1.00, 1.13)
NO_2	1.02 (0.99, 1.05)	1.03 (1.00, 1.06)	1.03 (1.00, 1.06)
BC	1.07 (1.03, 1.10)	1.08 (1.04, 1.11)	1.06 (1.03, 1.09)
O_3	1.01 (0.98, 1.05)	0.99 (0.96, 1.03)	0.99 (0.96, 1.03)
COVID-19 Hospitalization* (N= 1,563)			
PM_{25}	1.13 (0.97, 1.31)	1.11 (0.95, 1.30)	1.22 (1.04, 1.43)
NO_2	1.09 (1.01, 1.19)	1.05 (0.97, 1.14)	1.05 (0.96, 1.14)
BC	1.14 (1.05, 1.24)	1.10 (1.01, 1.20)	1.08 (0.99, 1.18)
O_3	0.93 (0.86, 1.01)	0.96 (0.88, 1.05)	0.96 (0.88, 1.05)
COVID-19 Mortality (N= 461)			
PM_{25}	1.18 (0.89, 1.57)	1.15 (0.86, 1.53)	1.18 (0.88, 1.59)
NO_2	1.02 (0.87, 1.18)	0.95 (0.81, 1.11)	0.95 (0.81, 1.10)
BC	1.09 (0.93, 1.27)	1.03 (0.88, 1.20)	1.02 (0.87, 1.19)
O_3	0.98 (0.83, 1.15)	1.03 (0.88, 1.22)	1.03 (0.88, 1.22)
All-cause Mortality (N= 5,098)			
PM_{25}	1.07 (0.98, 1.16)	1.02 (0.94, 1.11)	1.09 (1.00, 1.19)
NO_2	1.07 (1.02, 1.12)	1.00 (0.95, 1.05)	1.00 (0.96, 1.05)
BC	1.06 (1.01, 1.11)	1.00 (0.95, 1.05)	1.00 (0.95, 1.04)
O_3	0.93 (0.89, 0.98)	0.99 (0.94, 1.04)	0.98 (0.93, 1.03)

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: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 $\mu g/m^3$ for BC, 10 $\mu g/m^3$ for O_3.

Model 1 adjusted for calendar time (time axis), sex (male, female), and age at baseline (natural spline with four degrees of freedom); Model 2 additionally adjusted for civil status, household size, family income, and education; Model 3 further adjusted for parish-level mean income, unemployment rate.

Table A2: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 143,308 participants of the AIRCODEN-CPH cohort, when restricting to Copenhagen municipality.

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
COVID-19 Incidence* (N= 7,897)			
PM_{25}	0.98 (0.94, 1.02)	0.99 (0.96, 1.03)	1.02 (0.99, 1.06)
NO_2	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)	1.01 (0.99, 1.04)
BC	1.06 (1.03, 1.09)	1.06 (1.03, 1.08)	1.04 (1.01, 1.06)
O_3	1.02 (0.98, 1.06)	1.00 (0.97, 1.04)	0.99 (0.96, 1.03)
COVID-19 Hospitalization* (N= 1,122)			
PM_{25}	1.08 (0.98, 1.18)	1.06 (0.96, 1.16)	1.12 (1.02, 1.24)
NO_2	1.07 (1.01, 1.14)	1.04 (0.98, 1.11)	1.04 (0.98, 1.10)
BC	1.14 (1.06, 1.23)	1.10 (1.02, 1.19)	1.07 (0.99, 1.15)
O_3	0.89 (0.80, 0.98)	0.91 (0.82, 1.01)	0.89 (0.80, 0.98)
COVID-19 Mortality (N= 293)			
PM_{25}	1.07 (0.89, 1.29)	1.02 (0.84, 1.24)	1.06 (0.88, 1.29)
NO_2	1.02 (0.91, 1.15)	0.97 (0.86, 1.09)	0.97 (0.86, 1.09)
BC	1.09 (0.94, 1.26)	1.02 (0.88, 1.18)	1.00 (0.86, 1.16)
O_3	0.94 (0.77, 1.15)	1.00 (0.81, 1.22)	0.98 (0.80, 1.20)
All-cause Mortality (N= 3,634)			
PM_{25}	1.05 (0.99, 1.11)	1.01 (0.95, 1.06)	1.04 (0.99, 1.10)
NO_2	1.05 (1.01, 1.08)	1.00 (0.97, 1.04)	1.00 (0.97, 1.04)
BC	1.06 (1.02, 1.11)	1.01 (0.97, 1.05)	0.99 (0.95, 1.04)
O_3	0.93 (0.88, 0.98)	0.98 (0.92, 1.04)	0.96 (0.91, 1.02)

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: 5 $\mu g/m^3$ for $PM_{2.5}$, 10 $\mu g/m^3$ for NO_2, 0.5 $\mu g/m^3$ for BC, 10 $\mu g/m^3$ for O_3.
Model 1 adjusted for calendar time (time axis), sex (male, female), and age at baseline (natural spline with four degrees of freedom); Model 2 additionally adjusted for civil status, household size, family income, and education; Model 3 further adjusted for parish-level mean income, unemployment rate.

Table A3: Effect modification of the association between long-term exposure to air pollution and COVID-19 hospitalization among the 192,041 participants of the AIRCODEN-CPH cohort by sex, age, and individual-level SES characteristic at the cohort baseline on March 1, 2020.

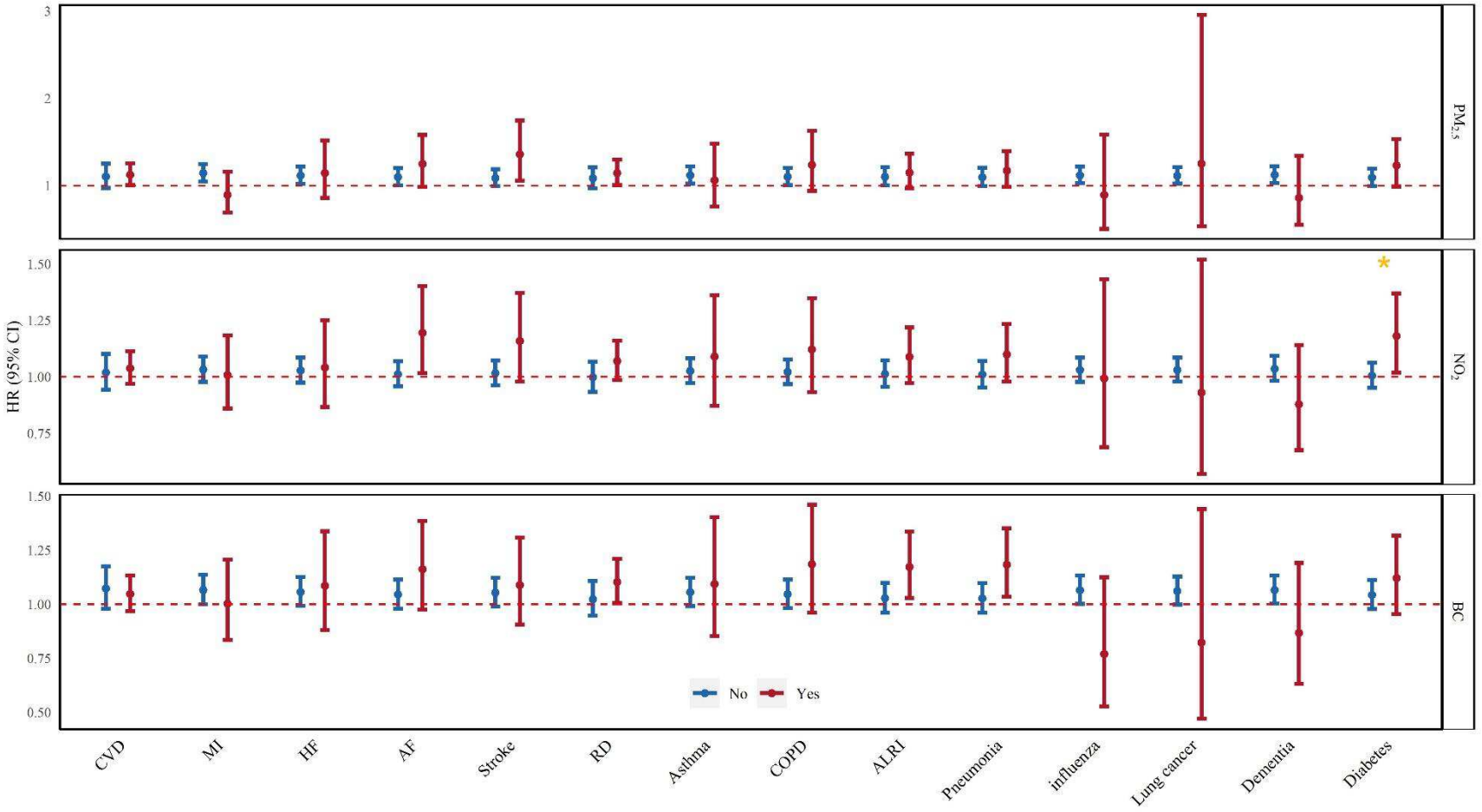
	PM2.5 HR (95% CI)	NO2 HR (95% CI)	BC HR (95% CI)	Global p-value
Age				
Less than 65	0.99 (0.84, 1.15)	0.99 (0.90, 1.08)	0.96 (0.86, 1.07)	$PM_{2.5}$: 0.08; NO_2: 0.29; BC: 0.05
65+	1.16 (1.05, 1.28)	1.05 (0.98, 1.11)	1.10 (1.02, 1.18)	
Sex				
Male	1.08 (0.97, 1.21)	1.03 (0.96, 1.10)	1.06 (0.98, 1.15)	$PM_{2.5}$: 0.45; NO_2: 0.99; BC: 0.96
Female	1.15 (1.02, 1.30)	1.03 (0.95, 1.11)	1.06 (0.96, 1.16)	
Country of Origin				
Denmark	1.10 (1.00, 1.22)	1.01 (0.95, 1.07)	1.02 (0.95, 1.09)	$PM_{2.5}$: 0.18; NO_2: 0.25; BC: 0.19
Western countries	0.77 (0.52, 1.15)	0.95 (0.74, 1.22)	1.07 (0.79, 1.45)	
Other countries	1.16 (0.97, 1.39)	1.12 (0.99, 1.26)	1.17 (1.02, 1.35)	
Married Status				
Unmarried	1.10 (0.88, 1.39)	1.07 (0.91, 1.25)	1.06 (0.88, 1.26)	$PM_{2.5}$: 0.83; NO_2: 0.68; BC: 0.56
Divorced	1.11 (0.94, 1.32)	0.99 (0.90, 1.09)	1.06 (0.94, 1.19)	
Widowed	1.19 (1.00, 1.43)	1.08 (0.96, 1.21)	1.14 (1.00, 1.31)	
Married	1.08 (0.95, 1.22)	1.02 (0.94, 1.10)	1.02 (0.93, 1.11)	
Income				
Low	1.21 (1.08, 1.36)	1.10 (1.02, 1.19)	1.16 (1.07, 1.27)	$PM_{2.5}$: 0.04; NO_2: 0.04; BC: 0.01
Middle	1.09 (0.93, 1.27)	0.99 (0.90, 1.09)	1.01 (0.91, 1.13)	
High	0.92 (0.77, 1.11)	0.94 (0.85, 1.05)	0.92 (0.81, 1.04)	
Education				
Missing	1.39 (0.94, 2.06)	1.17 (0.90, 1.51)	1.25 (0.92, 1.70)	$PM_{2.5}$: 0.18; NO_2: 0.94; BC: 0.88
Primary	1.12 (0.98, 1.30)	1.03 (0.94, 1.13)	1.06 (0.96, 1.18)	
Upper secondary	0.78 (0.56, 1.08)	0.98 (0.80, 1.21)	0.98 (0.77, 1.25)	

Vocational	1.06 (0.91, 1.23)	1.03 (0.93, 1.13)	1.06 (0.96, 1.18)	
Vocational Bachelor	1.19 (0.97, 1.45)	1.01 (0.90, 1.14)	1.03 (0.90, 1.18)	
College+	1.27 (0.96, 1.70)	1.05 (0.89, 1.24)	1.05 (0.85, 1.28)	
Household population				
1-2	1.12 (1.02, 1.22)	1.02 (0.97, 1.08)	1.06 (1.00, 1.14)	$PM_{2.5}$: 0.59; NO_2: 0.73; BC: 0.93
3-4	1.02 (0.80, 1.31)	1.04 (0.89, 1.22)	1.02 (0.85, 1.23)	
5+	1.29 (0.90, 1.85)	1.13 (0.89, 1.42)	1.06 (0.82, 1.38)	

HR=hazard ratio. CI=confidence interval. NO_2=nitrogen dioxide. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 μm. Results are presented for interquartile range increase: 2.67 μg/m^3 for $PM_{2.5}$, 6.25 μg/m^3 for NO_2, and 0.35 μg/m^3 for BC.

*Wald test was used to calculate the global P-value.

Figure A1: Effect modification of the association between long-term exposure to air pollution and COVID-19 hospitalization among the 192,041 participants of the AIRCODEN-CPH cohort by co-morbidities 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. Results are presented for interquartile range increase: 2.67 µg/m^3 for $PM_{2.5}$, 6.25 µg/m^3 for NO_2, and 0.35 µg/m^3 for BC. *Wald test was used to calculate the global P-value, and results with P-value <0.05 are highlighted with a star.