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Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalization or death: Danish nationwide cohort study

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Abstract

Objective: Early ecological studies have suggested links between air pollution and risk of COVID-19, but evidence from individual-level cohort studies is still sparse. We examined whether long-term exposure to air pollution is associated with risk of COVID-19 and who is most susceptible.

Methods: We followed 3,721,810 Danish residents ≥ 30 years on March 1st 2020 in the National COVID-19 Surveillance System until the date of 1st positive test (incidence), COVID-19 hospitalization or death until April 26th 2021. We estimated residential annual mean particulate matter < 2·5 μm in diameter ($PM_{2·5}$), nitrogen dioxide (NO_2), black carbon (BC), and ozone (O_3) in 2019 by the Danish DEHM/UBM model, and used Cox proportional hazards regression models to estimate the associations of air pollutants with COVID-19 outcomes, adjusting for age, sex, individual- and area-level socioeconomic status, and population density.

Results: 138,742 were infected, 11,270 hospitalized and 2,557 died from COVID-19 during 14 months. We detected associations of $PM_{2.5}$ (per 0·5 μg/m^3) and NO_2 (per 3·6 μg/m^3) with COVID-19 incidence (hazard ratio; 95% confidence interval: 1·10; 1·05-1·14 and 1·18; 1·14-1·23), hospitalizations (1·09; 1·01-1·17 and 1·19; 1·12-1·27), and death (1·23; 1·04-1·44 and 1·18; 1·03-1·34), which were strongest in the lowest socioeconomic groups and among patients with chronic respiratory, cardiometabolic, and neurodegenerative disease. We found positive associations with BC and negative with O_3.

Conclusion: 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.

Keyword: air pollution, COVID-19, SARS-CoV-2, hospitalization, incidence, mortality

Introduction

Identifying 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 disease 2019 (COVID-19) or worsen the severity of the health outcomes among individuals with COVID-19 is crucial for the management of the current COVID-19 pandemic and preparing for future similar pandemics. Air pollution is the major environmental stressor and 4th global risk factor for morbidity and mortality, after smoking, high blood pressure and diet, causing 6,7 million deaths in 2019.[1] Several biologically plausible mechanisms explain how air pollution may increase the risk of COVID-19. Long-term exposure to air pollution may increase vulnerability to the SARS-CoV-2 indirectly, by increasing the risk of respiratory and cardio-metabolic diseases,[1] which increase the risk of severe COVID-19,[2–5] or directly by compromising immune responses.[6] The link between air pollution and COVID-19 is supported furthermore by air pollution link with other respiratory infections including pneumonia.[7–10]

Early ecological studies[11] raised headlines postulating that air pollution increases the risk of COVID-19, despite the potential fallacies of this designs.[12] Epidemiological evidence based on the cohort studies with individual-level data on exposure to air pollution and later onset of COVID-19 is still sparse and mixed, yet crucial in understanding the impact of air pollution on contracting the SARS-CoV-2 and developing of the COVID-19 disease. Only three studies examined incidence of SARS-CoV-2 infection in general population. A study from Varese, Italy detected association of long-term exposure to particulate matter < 2.5 μm in diameter ($PM_{2.5}$) with COVID-19 incidence,[2] a study from Rome found no association of $PM_{2.5}$ or nitrogen dioxide (NO_2) with incidence, but detected associations with COVID-19 mortality,[13] and a study in UK Biobank detected association of $PM_{2.5}$ and NO_2 with

incidence, but none with COVID-19 hospitalizations or death.[14] In addition, a Barcelona study found no association of $PM_{2.5}$ or NO_2 with SARS-CoV-2 positive serum test, but detected associations with self-reported COVID-19, that were strongest with severe outcomes (hospitalization or death).[15] Furthermore, nine studies with data on SARS-CoV-2 cases only [16-24], reported association between $PM_{2.5}$ and increased risk of severe COVID-19 outcome in terms of hospitalizations,[16–18, 20-22] intensive care unit (ICU) admission,[17,19, 20] or death.[17,19,20, 23]. One study has showed associations between $PM_{2.5}$ and increased risk of dying in a population patients hospitalized with COVID-19 [24].

In this large nationwide study from Denmark, we examined whether long-term exposure to air pollution is associated with risk of SARS-CoV-2 infection, hospitalization, and death, and identified those who were most susceptible by sex, age, socio-economic status (SES) and co-morbidities.

Methods

Study Population and COVID-19 outcome definitions

We created a population-based nationwide cohort (AIRCODEN) by including all Danish residents 30 years or older on March 1, 2020 and lived in Denmark for at least one year prior to this date. Using the unique personal identification number, we linked the AIRCODEN to the National COVID-19 Surveillance System, with information on SARS-CoV-2 PCR test date, test result, hospital admission date, and death date. PCR testing, and in the second pandemic wave after August 1st, 2020 lateral flow testing, in Denmark was offered to all citizens free-of-charge with easy access and self-booking opportunities. The positive lateral flow test had to be confirmed by PCR test in order to be registered in the National COVID-19 Surveillance System, so only PCR confirmed COVID-19 cases are considered in this study.

We defined three COVID-19 outcomes, as defined by the National COVID-19 Surveillance System: incidence (first positive test), hospitalization (inpatient admission, including emergency room admission from any cause, for > 12 hours within 14 days after the first positive test), and death from any cause (within 30 days of the first positive test). We also evaluated all-cause and non-COVID-19 mortality, to examine whether air pollution-all-cause mortality association during pandemic period is comparable to that observed before the pandemic.[20] We defined two pandemic waves reflecting two distinct periods, with respect to testing capacity and preventive (lockdown) measures: first pandemic wave (1st March – 1st August 2020) reflects period with very limited testing capacity and full lockdown, and second wave starting on 1st August 2020, reflects period with full opening of the society along with significant improvement of testing capacity and opening of testing centers. We extracted individual-level SES information in 2019, including employment, education, income, wealth, marital status, and household size from socio-economic registers at Denmark Statistics, and defined parish- and municipality-level SES. There are 2,163 parishes and 96 municipalities in Denmark. In addition, there are five administrative regions in Denmark, which run secondary health care system (set our strategies for handling COVID-19 in the hospitals, hospital capacity, etc.), and COVID-19 testing strategy and testing capacity. Thus, in this analyses we have adjusted for regions in COVID-19 analyses, to account for different COVID-19 strategies in the five regions, but not in all-cause mortality analyses, which is not affected by regional handling of secondary health care, and consistent with our previous analyses on air pollution and all-cause mortality (So et al. 2020). Co-morbidities were defined as any hospital contact (inpatient admission, emergency room admission, or outpatient visit) in the Danish National Patient Register prior to March 1, 2020 (table S1).

Air Pollution Exposure

We used the Danish DEHM/UBM model estimates of annual means of NO_2, $PM_{2.5}$, PM_{10}, BC, and O_3 at a 1x1 km resolution in the period 1979-2019. This validated [27–29] model consists of the chemistry-transport model, the Danish Eulerian Hemispheric Model (DEHM)[21], and the Urban Background Model (UBM),[27] including several domains with different spatial resolutions to calculate intercontinental, regional and local transport of air pollution. The models were successfully validated against measurements. In addition, we used the European-wide hybrid LUR model, developed within the Effects of Low-Level Air Pollution: A Study in Europe (ELAPSE) project, which provides annual means of $PM_{2.5}$, NO_2, BC, and O_3 (warm season) in 2010 at a 100x100m resolution,[30] recently linked to all-cause mortality in Europe[31,32] and Denmark.[25] In brief, the LUR model utilized routine monitoring data from the European Environment Agency AirBase for $PM_{2.5,}$ NO_2 and ozone, and the European Study of Cohorts for Air Pollution Effects (ESCAPE) monitoring data for BC. Satellite data, chemistry-transport 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.[30]

Statistical Analysis

We used Cox proportional hazard models (for time-to-event data) with calendar time as underlying timescale to examine the associations of air pollutants with COVID-19 incidence, hospitalization, death, or all-cause mortality (separately), censoring at the date of death from other causes (except for all-cause mortality where all deaths are outcome), emigration, or the end of follow-up on April 26, 2021, whichever came first. We fitted four models: Model 1: adjusted for age (strata, five-year band), sex (strata), and region (strata, five administrative regions in Denmark; not included in all-cause mortality analyses); Model 2: additionally adjusted for individual-level SES, including marital status, highest completed education,

occupational status, individual wealth (tertile), family income (tertile), household size; Model 3 (main model): additionally adjusted for population-level SES including parish-level population density, municipality-level access to health care (the number of general practitioners/citizens), parish-level SES factors: mean income, median wealth, % unemployment, % primary or low education, and the SES difference between municipality and parish, and Model 4: additionally adjusted for monthly municipality-level SARS-CoV-2 positive rate (PCR tests), using time-varying Cox models, in order to adjust for spatio-temporal COVID-19 pandemic development.

We fitted single pollutant models using mean exposure in 2019 (main analyses), three-year (2017-19) and ten-year (2010-2019) means of pollutants estimated by the Danish DEHM/UBM model, and 2010 mean exposure estimated by ELAPSE model. We estimated exposure-response functions using natural cubic splines with three degrees of freedom. We estimated associations in a subsample of population below predefined levels of pollutants, to examine associations at the lower end of exposure. Effect modification of an association of $PM_{2.5}$ and NO_2 with COVID-19 by 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, a multiplicative scale test for the difference between the subgroups of subjects defined by these effect modifiers. We fitted two-pollutant models for pollutant combinations with the Pearson correlation coefficient below 0.7.

We performed several sensitivity analyses. To evaluate confounding by missing information on smoking and body mass index (BMI), we additionally adjusted for parish-level prevalence

rates of chronic obstructive pulmonary diseases (COPD) or lung cancer (proxies for smoking) and diabetes (obesity proxy), and applied the Shin indirect adjustment method,[28] using the associations of air pollution with smoking and BMI based on the Danish National Survey. We estimated associations in as subsample of the population tested for SARS-CoV-2, to explore whether associations with air pollution are affected by a selection bias in who gets tested, We estimated associations in a subsample of population, as this is a selected sample, and not directly comparable to entire population. In addition to all-cause, we estimated associations of air pollutants with non-COVID-19 all-cause mortality. We examined the stability of the associations over time and whether they were affected by changes in testing capacity, stringency of and compliance with pandemic measures (lockdown, wearing mask, distancing, etc.) by estimating associations separately in two pandemic waves (March 1-July 31, 2020; August 1, 2020-April 26, 2021).

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

Results

Of the 3,743,013 subjects 30 years or older and Danish residents on March 1, 2020, we excluded 8,397 with missing information on air pollution, 676 on individual SES, 12,127 on parish SES, and three with SARS-CoV-2 positive test before March 1, 2020 leaving 3,721,813 subjects for final analyses. During 14 months of follow-up (411-417 days) and 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, whereas 62,359 individuals died in total Compared to the total population, subjects who died or were hospitalized with COVID-19, or

died from any cause, were less likely to be women, highly educated, employed, be married, or have a high income (Table 1). Similar patterns, but with less pronounced differences were observed with incident COVID-19 cases. The strongest positive correlation was observed between NO_2 and BC (0.75), reflecting same source – traffic, followed by NO_2 and $PM_{2.5}$ (0.61) (figure S1). Strongest negative correlation was observed between NO_2 and O_3 (-0.86) (figure S1). Traffic-related NO_2 and BC are highest in the urban areas of Denmark, whereas O_3 is highest in the rural areas. $PM_{2.5}$ in Denmark is apart from urban areas also high in Southeastern Denmark due to long-range transported particles from Central/Eastern Europe (figure S2).

We detected strong and significant positive associations of $PM_{2.5}$, NO_2 and BC with all three COVID-19 outcomes (Table 2), strongest for mortality, with 23% and 18% higher risk of COVID-19 death for each 0.53 and 3.59 $\mu g/m^3$ increase in $PM_{2.5}$ and NO_2, respectively. Weaker (half of those with mortality) associations were found for $PM_{2.5}$ and PM_{10} and COVID-19 incidence and hospitalizations, whereas associations with NO_2 and BC were almost identical for three outcomes. We found negative associations of O_3 with three COVID-19 outcomes and no association of PM_{10} or O_3 with all-cause mortality. The HRs attenuated most after area-level covariates adjustment, whereas additional adjustment for municipality-level SARS-CoV-2 positivity rates didn't affect estimates.

Compared to one-year, HRs were almost identical with three- and ten-year exposure windows of all air pollutants (figure S3). Associations with air pollution estimated by ELAPSE model (table S2), which showed moderate correlation with the Danish model (for example, correlation of 0.51 between $PM_{2.5}$ from two models and 0.63 for NO_2 from the two models) (figure S4), were comparable to those observed with the Danish model(figure S5): slightly

weaker for $PM_{2.5}$, NO_2, and O_3, and stronger for BC. We have also observed considerably wider CIs with the Danish model than with the ELAPSE model (figure S5). Exposure-response functions (ERF) were linear or curvilinear for most of the pollutants and COVID-19 outcomes, though notably with weaker associations for $PM_{2.5}$ and COVID-19 incidence below 7 $\mu g/m^3$, and none for NO2 and COVID-19 incidence below 8 $\mu g/m^3$.We also note limitation of estimating associations in these lower exposure ranges where data are more sparse. We found generally stronger associations at lower exposure levels (figure S6, table S3).

In the two-pollutant models, associations with NO_2 and BC were robust to adjustment for $PM_{2.5}$, with COVID-19 incidence and hospitalization, while for COVID-19 mortality, results seemed most robust for $PM_{2.5}$ (table S4). Associations remained unchanged after indirect adjustment for smoking and BMI (figure S7), in population of those tested (figure S8), and for non-COVID-19 mortality (table S5). We found no associations in the first, but significant positive associations in the second pandemic wave (figure S9).

We found stronger associations of $PM_{2.5}$ and NO_2 with COVID-19 incidence in those with lower SES, and living in households with >4 inhabitants (Figure 2), and in those with prior CVD, RD, ALRIs, lung cancer, dementia and diabetes (Figure 3), with similar trends but weaker associations for COVID-19 hospitalization, and no effect modification with COVID-19 mortality, notably limited by small number of cases (figure S10-13).

Discussion

In this large nationwide study, we detected strong associations between long-term exposure to air pollution and contracting SARS-CoV-2 infection and developing severe COVID-19

resulting in hospitalization or death. People with chronic cardio-metabolic and respiratory diseases, dementia and prior ALRIs and those who are the most socioeconomically disadvantaged were most vulnerable.

Our findings generally agree with three other studies on long-term exposure to air pollution and COVID-19 incidence, hospitalization or mortality, although with notable inconsistencies between studies. [2,13–15] Our results corroborate Veronesi et al. who in 62,848 residents of Varese (4,408 positive in first pandemic year) detected 5.1% increase in COVID-19 rate for each $\mu g/m^3$ increase in $PM_{2.5}$.[2] Sheridan et al. has in 424,721 subjects from UK Biobank (10,790 positive March 16- 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 findings, found no associations with COVID-19 hospitalizations (n=1,598) or deaths (n=568).[14] Nobile et al. has in 1,594,308 subjects from Rome (79,976 positive and 2,656 deaths January 1, 2020- April 15, 2021) 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.[13] Furthermore, our results agree with Kogevinas et al. who found associations with COVID-19 risk assessed in 9,000 subjects by blood serum tests, self-reports, hospitalizations, and death.[15] Our finding of stronger associations with increasing severity of COVID-19 was also observed by Kogevinas et al.[15] and Nobile et al.,[13] but not by Sheridan et al.[14] We detect very strong associations with COVID-19, that of 10% increase in incidence and 23% in COVID-19 mortality per 0.53 $\mu g/m^3$ in $PM_{2.5,}$ substantially stronger than those in above mentioned studies, but in line with early ecological studies.[11] Our association with COVID-19 mortality is 10 times that observed for $PM_{2.5}$ and all-cause mortality (23% vs 2%) (Table 2), in line with Nobile et al. who reported eight times higher estimate for COVID-19 than for non-COVID-19 deaths (8% vs. 1% per 0.92

μg/m^3).[13] These strong associations may in part be explained by the residual confounding by smoking, BMI and other lifestyle factors, as observed in Sheridan et al,[14] or other unmeasured confounders. Strong associations may also be due to fact that the risk of all-cause mortality due to $PM_{2.5}$ and NO_2 is much higher in those ever tested than the general population (figure S8), likely showing that those at higher risk of death are those being more tested. These strong associations may however, be plausible, as we have earlier reported considerably stronger associations of $PM_{2.5}$ with all-cause mortality in Denmark than in other European countries,[31] almost three times stronger than those in the Roman cohort utilized in Nobile et al. study.[13] Furthermore, our finding of stronger associations at the lowest exposure supports stronger associations with COVID-19 in Denmark, with the low air pollution levels, as for all-cause mortality[20,31,32], than those observed in more polluted Italy, Spain and UK.[2,13–15] However, some caution in interpreting our findings should be noted due to the Danish model DEHM/UBM estimates being less precise that the ELAPSE estimates (figure S5), and that the large estimates could be more of a reflection of larger uncertainty (wider CIs) rather than only strength of association. Notably, our findings were robust to adjustment for COVID-19 positivity and its geographical development over time, as the only study to date able to evaluate confounding by COVID-19 development over time. Furthermore, our study is unique in being able to utilize alternative air pollution exposure, which showed consistent results to main analyses. Finally, our results were robust to limiting population to tested individuals, together with other sensitivity analyses, supporting the plausibility of the observed associations (figure S3 and S5). Our results on air pollution leading to increased risk of contracting COVID-19 are also in line with larger literature showing that the long-term exposure to air pollution increases risk of more severe COVID-19 outcome in those who contracted COVID-19 [16-24].

We found negative associations of O_3 with all three COVID-19 outcomes in agreement with two studies that had data on O_3 [2,15]. Veronesi et al. also found significant negative associations of O_3 with COVID-19 incidence [2], as did Kogevinas et al. with all COVID-19 outcomes he considered[2,15]. The negative associations we found might reflect the high negative correlation with especially NO_2 and BC (figure S1), traffic pollutants which may the most relevant for the COVID-19, as suggested by two-pollutant models (figure S4). O_3 and NO_2 are negatively correlated because when O_3 is close to combustion sources (eg, major roads), it reacts with nitric oxide emitted from the combustion source to form oxygen and NO_2. O_3 therefore tends to be low near roadways, whereas BC emitted by traffic is high. NO_2 is in part directly emitted from traffic and in part formed by the atmospheric reactions, so it is also high near roadways.

Although exact molecular mechanisms by which air pollution affects viral infection and pathogenesis of COVID-19 remain unknown, there are several plausible pathways[6]. Exposure to air pollution may promote upregulation of the angiotensin converting enzyme-2 (ACE2) receptor relevant for viral entry, replication and assembly, and 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[6]. 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 number of organs, including the lungs, heart, kidney, and brain, resulting in death.[6] Furthermore, air pollution likely

additionally increases risk of COVID-19 severity and death indirectly by increasing risk of major respiratory and cardio-metabolic diseases,[1] that in turn increase COVID-19 severity/mortality. [2–5]

We show, for the first time, highest vulnerability to air pollution among those with lowest SES, in part likely explained by indirect impact of lifestyle, such as smoking, obesity, physical inactivity, etc. linked with COVID-19 incidence.[5,14] Another explanation for stronger association in lowest SES is likely related to the lack of social support to lockdown, overcrowding, and higher exposure. Furthermore, low SES is related to work in occupations that were exempt from lockdowns and working from home options, such as cleaning, security and service workers, bus drivers, etc. resulting in higher exposure to COVID-19 etc. Enhanced vulnerability to air pollution in large households likely reflects exposure to higher doses of virus and higher risk of infection. We also report vulnerability in chronic disease patients, in line with Veronesi et al. who found stronger associations in coronary heart and obstructive lung disease patients,[2] but with limited statistical power. We also note that effect modification results pointing to higher vulnerability of chronic disease patients could be a reflection of more frequent testing among these individuals, considered to have higher risk of infection or severe outcomes.

We find that associations of air pollution with COVID-19 were limited to the second pandemic wave. most likely explained by testing capacity with some effects from background non-pharmaceutical interventions[34] as well as behavioral modification. We should note that comparison of the results from the two demands some caution, as the two pandemic waves in Denmark are substantially different, presenting different stages of the pandemic and viral spread, prevention measures, testing capacity, as well as differences in personal behavior and

lifestyle. Only a very limited number of COVID-19 cases was detected in the first pandemic wave, notably those who travelled to Denmark from hot spot areas abroad (first cases in Denmark were tourists from ski areas in Italy and Austria) early in the pandemic and near contacts (family, work colleagues, friends) to those infected. It is likely that these early infections of highly new infectious virus in the completely closed society and controlled pandemic, were likely spreading by other mechanisms than air pollution, mainly close contacts. Second pandemic wave is characterized by large improvement in testing capacity (testing offered only to those with severe symptoms or close contacts to cases in the first wave) free of charge to all, introduction of masks, and reopening of the society (opening of work places, restaurants, theaters, cinemas, etc. conditional on negative test). Thus in the second wave, when society was completely reopen and testing introduced for all, virus infection developed and took its' natural course resulting in many more people being infected, and in this more open and 'normal' pandemic dynamic, a fraction of COVID-19 infections seemed to be driven by air pollution. Another explanation may be found in the new EU1 SARS-CoV-2 variant, which dominated the second wave in Denmark [35].

Our study is the largest to date and the first nationwide analyses of long-term exposure to air pollution and risk of COVID-19, facilitated by the internationally unique access to high-quality, centrally collected, individual-level Danish COVID-19 surveillance data for the entire population, in combination with national health, demographic and SES registers, and historical data on air pollution. As Denmark had one of the most intense testing strategies, with testing free of charge and easily accessible, we have arguably, especially in the second wave of pandemic, been able to determine the most complete definition of incidence of SARS-CoV-2 infection, as more than 80% of the population was tested in the first 14 months of the pandemic, many multiple times. acknowledging limitations of this approach study

benefited from detailed data on co-morbidites, SESm and spatio-temporal changes in COVID-19 pandemic positivity rates, and it is to provide the first and the most comprehensive analyses of who is most susceptible to air pollution related risk of COVID-19.

Major limitation of our study was lack of data on smoking, physical activity, BMI, diet, and nursing homes residence. Notably, Denmark managed COVID-19 pandemic exceptionally well with only minor excess mortality, and without large COVID-19 mortality clusters in nursing homes as seen elsewhere.[36] Our definition of SARS-CoV-2 incidence is only partial, as Danish 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, hospitalized patients, etc. The testing policy was massively expanded in the second wave, where testing free of charge was offered to all, and when a large portion of the population was tested daily, as negative test was required to enter workplaces, universities, schools, restaurants, movie theaters, etc. We did not have data on vaccinations, and could not address whether vaccination would have affected observed associations. As vaccination was first introduced in Denmark at the end of the study, it would likely have had minor impact on observed associations. First vaccination in Denmark was given on December 27th, 2020, and only a fraction (9%) of population (health care workers, the elderly and chronic disease patients) was vaccinated by April 26th, 2021, the end of follow-up in this study. Another limitation is the definition of comorbidities based on the hospital contact data only. This is major limitation for some outcomes, such as ALRIs, for example, as only a fraction of more severe ALRIs are captured, and not those treated by general practitioner for example, or those untreated. For chronic diseases such as major cardio-metabolic diseases, lung cancer, and dementia, this hospital contact definition captures better true prevalence in the population, than for ALRIs. Limitations in our exposure data

include larger uncertainty in the effect estimates (wider CIs) with the Danish model DEHM/UBM than in those with the ELAPSE model (figure S5), and the possibility that large estimates could be more of a reflection of lower precision rather than only strength of association. Also some inconsistencies, most pronounced for BC, between two exposure models are also noted as the weakness. However, both exposure models, even where size and the precision of the observed associations differ, clearly show consistently associations with all three COVID-19 outcomes, for all three pollutants, supporting plausibility of air pollution link with COVID-19. Finally, we only had data for annual mean of O_3 in our main analyses with Danish exposure model, whereas warm season average should be better predictor of health relevant exposures. However, our results are consistent with those for warm season O_3 from ELAPSE model (figure S5).

Conclusion

In a nationwide Danish study of the first 14 months of the COVID-19 pandemic, we found that long-term exposure to air pollution at low levels, well below current EU limit values, is associated with increased risk of contracting SARS-CoV-2, and developing severe COVID-19 disease demanding hospitalization or resulting in death. Chronic cardio-metabolic, respiratory and neurodegenerative disease patients, individuals with prior ALRIs, and the lowest SES groups appear most susceptible and most likely to contract SARS-CoV-2 or develop COVID-19 due to air pollution. These findings contribute important new data to an increasing evidence base showing that air pollution is a risk factor for COVID-19.

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Author Contributions

Study was conceptualized and designed by Zorana J. Anderson and Jiawei Zhang. Statistical analysis was conducted by Jiawei Zhang, and Youn-Hee Lim helped with data management and statistical analysis. Rina So helped with indirect adjustment for missing confounders analysis. Jeanette T. Jørgensen helped with preparing the COVID-19 data for the analysis. Matthias Ketzel and Jørgen Brandt developed the Danish DEHM/UBM model, Gerard developed the ELAPSE model. Zorana J. Andersen and Jiawei drafted the manuscript. All authors have read and revised the manuscript and contributed to the interpretation of the results. All authors have approved the final draft of the manuscript.

Conflict of interest

All authors disclose that there are no potential competing financial interests or personal relationships that could affect the work reported in this article.

Table 1: 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%)	0,119 (4.65%))	4,247 (6.81%))
Married/Partner, n (%)	2,069,552 (55.6%)	84,220 (60.7%)	6,019 (53.4%)	0,991 (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%)	0,815 (31.9%)	18,717 (30.0%)
High, n (%)	1,394,038 (37.5%)	54,926 (39.6%)	2,596 (23.0%)	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%)	0,742 (6.6%)	0,099 (3.9%)	2,436 (3.9%)
Wealth					
Low, n (%)	1,072,333 (28.8%)	47,463 (34.2%)	2,175 (19.3%)	0,202 (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					
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					
$PM_{2.5}$ (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

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

Table 2: 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.

	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3* HR (95% CI)	Model 4 HR (95% CI)
COVID-19 Incidence* (N=138,742)				
$PM_{2.5}$	1.16 (1.12-1.21)	1.23 (1.18-1.27)	1.10 (1.05-1.14)	1.09 (1.05-1.12)
NO_2	1.25 (1.20-1.30)	1.32 (1.27-1.37)	1.18 (1.14-1.23)	1.15 (1.11-1.18)
BC	1.07 (1.03-1.10)	1.07 (1.04-1.11)	1.05 (1.01-1.08)	1.04 (1.01-1.07)
O_3	0.82 (0.80-0.85)	0.79 (0.77-0.81)	0.86 (0.84-0.89)	0.90 (0.88-0.92)
PM_{10}	1.05 (1.01-1.08)	1.07 (1.04-1.11)	1.09 (1.06-1.12)	1.06 (1.03-1.09)
COVID-19 Hospitalization* (N=11,270)				
$PM_{2.5}$	1.22 (1.15-1.30)	1.24 (1.17-1.32)	1.09 (1.01-1.17)	1.09 (1.02-1.17)
NO_2	1.35 (1.27-1.44)	1.35 (1.28-1.43)	1.19 (1.12-1.27)	1.15 (1.08-1.22)
BC	1.08 (1.04-1.12)	1.08 (1.04-1.12)	1.05 (1.01-1.08)	1.04 (1.01-1.08)
O_3	0.77 (0.74-0.81)	0.77 (0.74-0.81)	0.86 (0.82-0.91)	0.89 (0.85-0.94)
PM_{10}	1.10 (1.03-1.17)	1.10 (1.04-1.17)	1.14 (1.07-1.20)	1.08 (1.03-1.14)
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)	1.22 (1.04-1.43)
NO_2	1.34 (1.21-1.49)	1.29 (1.16-1.42)	1.18 (1.03-1.34)	1.12 (0.98-1.28)
BC	1.09 (1.05-1.14)	1.09 (1.05-1.13)	1.06 (1.02-1.10)	1.05 (1.00-1.09)
O_3	0.78 (0.72-0.84)	0.80 (0.74-0.87)	0.87 (0.78-0.96)	0.92 (0.82-1.02)
PM10	1.15 (1.04-1.27)	1.13 (1.02-1.25)	1.19 (1.07-1.33)	1.13 (1.01-1.26)
All-cause Mortality (N=62,359)				
$PM_{2.5}$	1.02 (1.00-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.02)
NO_2	1.05 (1.02-1.08)	1.04 (1.02-1.06)	1.04 (1.01-1.07)	1.03 (1.02-1.05)
BC	1.02 (1.01-1.04)	1.02 (1.01-1.03)	1.01 (1.00-1.02)	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)	1.00 (0.99-1.02)
PM_{10}	0.99 (0.97-1.00)	0.96 (0.95-0.98)	0.98 (0.96-0.99)	0.98 (0.97-0.99)

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. Results are presented for interquartile range increase: 0.53 $\mu g/m^3$ for $PM_{2.5}$, 3.59 $\mu g/m^3$ for NO_2, 0.09 $\mu g/m^3$ for BC, 2.79 $\mu g/m^3$ for O_3, and 1.14 $\mu g/m^3$ for PM_{10}.
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 (Main model) 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 health care; Model 4 (time-varying Cox) additionally adjusted for municipality-level monthly COVID-19 positive rates as a proxy for spatial and temporal pandemic development (analysis for all-cause mortality did not stratified by regions).
*N=3,721,810 (three people excluded due to COVID-19 infection before baseline on March 1, 2020).

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Figure Legends

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.

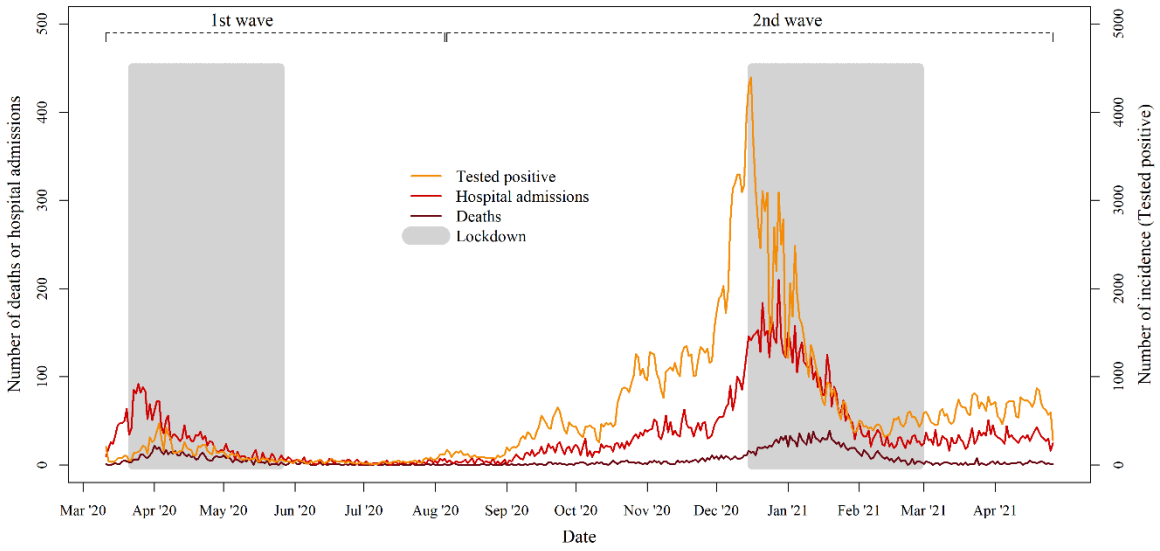
Figure 2: Effect modification* of the association between long-term exposure to air pollution and COVID-19 incidence among the 3,721,810 participants of the AIRCODEN cohort by sex, age, and individual-level SES characteristic at the cohort baseline on March 1, 2020.

HR=hazard ratio. CI=confidence interval. NO_2=nitrogen dioxide. $PM_{2·5}$=particulate matter with diameter ≤ 2·5 μm. Results are presented for interquartile range increase: 0·53 μg/m^3 for $PM_{2·5}$ and 3·59 μg/m^3 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 3: 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 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. CVD=cardiovascular disease. MI=myocardial infarction. HF=heart failure. AF=atrial fibrillation. RD=respiratory disease. COPD=chronic obstructive pulmonary disease. ALRI=acute lower respiratory infection. Results are presented for interquartile range increase: 0·53 μg/m^3 for $PM_{2·5}$ and 3·59 μg/m^3 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.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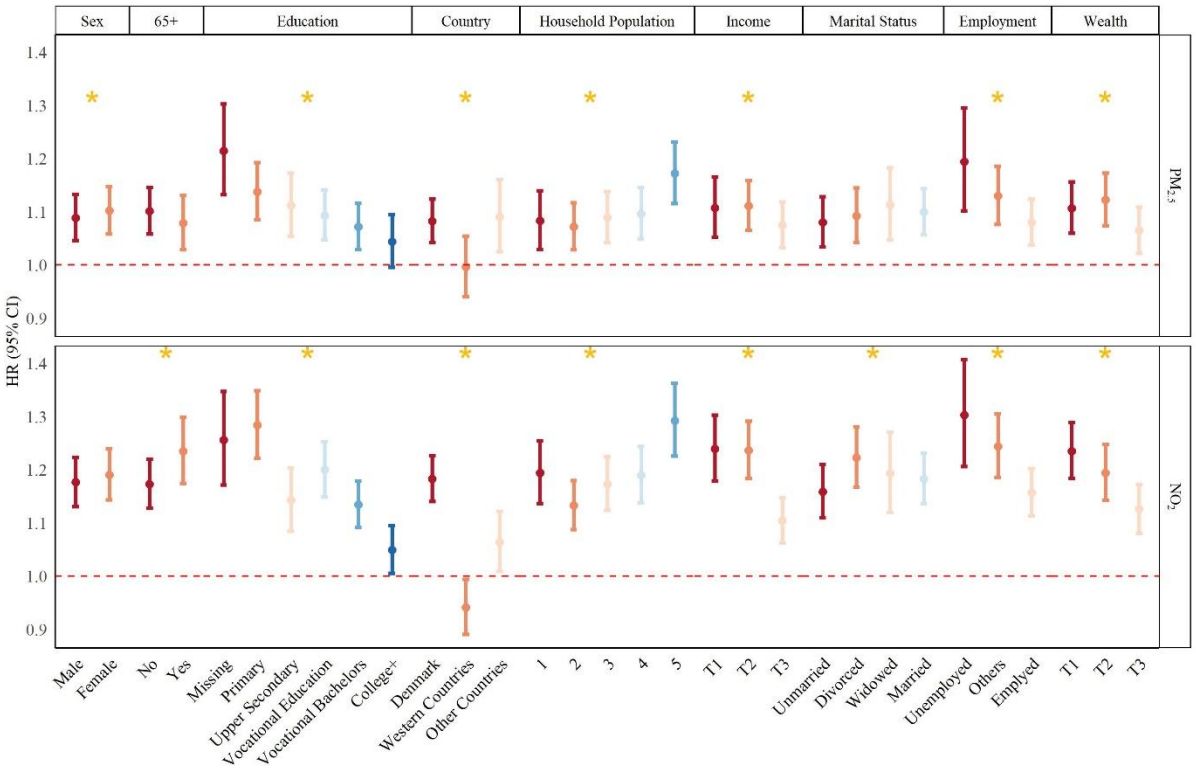
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NO2
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Female
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Missing
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Upper Secondary
Vocational Education
Vocational Bachelors
College+
Denmark
Western Countries
Other Countries
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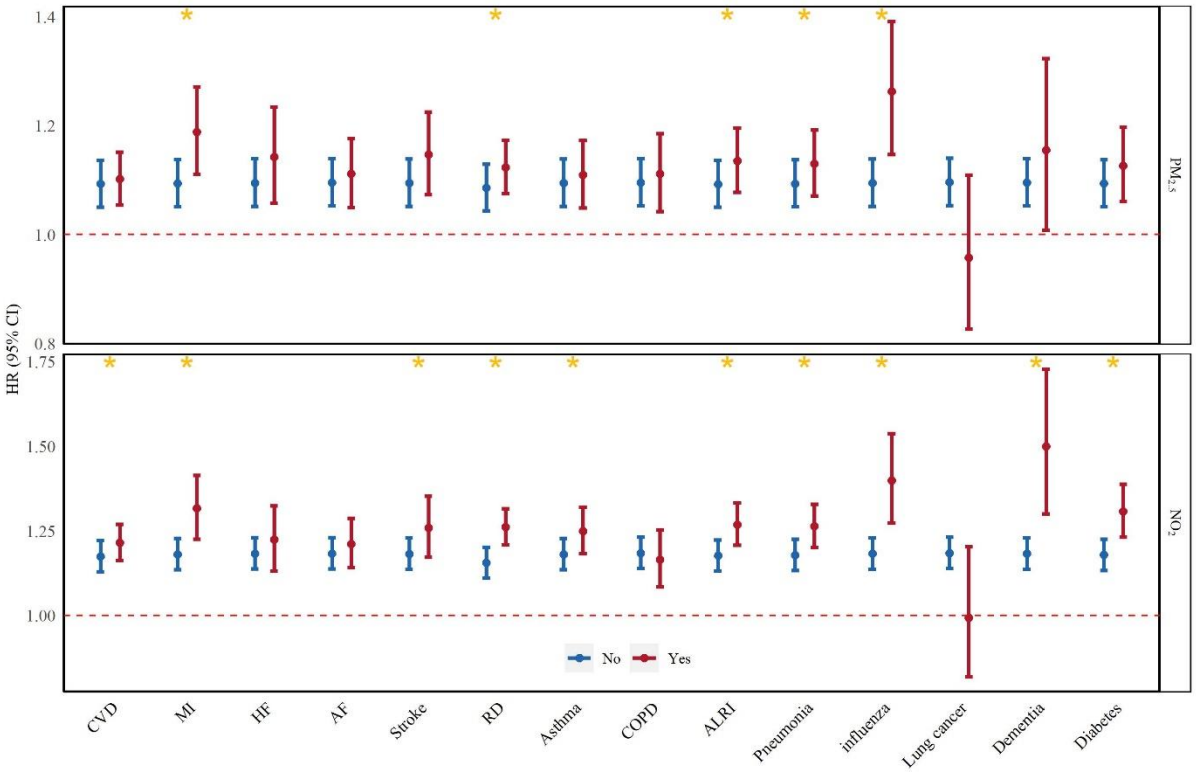
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Yes
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HF
AF
Stroke
RD
Asthma
COPD
ALRI
Pneumonia
influenza
Lung cancer
Dementia
Diabetes

Supplementary Material

Long-term exposure to air pollution and risk of SARS-CoV-2 infection and COVID-19 hospitalization or death: Danish nationwide cohort study

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Table of Contents

Table S1: Definition and prevalence of co-morbidities among the 3,721,813 participants of the AIRCODEN cohort at the study baseline on March 1, 2020. 1

Figure S1: Pearson correlation coefficients between annual mean air pollution levels at residence in 2019 among the 3,721,813 participants of the AIRCODEN cohort. 2

Figure S2: Annual parish mean levels of $PM_{2.5}$, NO_2, BC and O_3 in 2019 in Denmark among the 3,721,813 participants of the AIRCODEN cohort. 3

Figure S3: 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 different exposure windows of 1-year mean (2019), 3-year mean (2017-2019), and 10-year mean (2010-2019). 4

Table S2: The summary of the air pollution level estimated by DEHM/UBM model in 2019 and the ELAPSE model in 2010 among the 2,205,957 participants of the AIRCODEN cohort who had data on both exposures. 5

Figure S4: 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. 6

Figure S5: 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 two different exposure assessment models: DEHM/UBM model in 2019 and the ELAPSE model in 2010. 7

Figure S6: 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. 8

Table S3: The association between long-term exposure to air pollution and COVID-19 related morbidity and mortality below various cut-off values. 10

Table S4: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality among the 3,721,813 participants of the AIRCODEN cohort: two pollutant models. 11

Figure S7: 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 with additional adjustment for missing information on individual lifestyle[*]. 12

Figure S8: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the subset of 2,902,932 participants of the AIRCODEN cohort who were tested for COVID-19 (excluding 818,881 (22%) participants who were never tested for COVID-19 in the study period from March 1, 2020 until April 26, 2021). 13

Table S5: The association between long-term exposure to air pollution and all-cause mortality as well as non-COVID-19 mortality among the 3,721,813 participants of the AIRCODEN cohort. 14

Figure S9: 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 in two pandemic waves: March 1-July 31, 2020 (red) and August 1, 2020-April 26, 2021 (blue). 15

Figure S10: Effect modification[*] of the association between long-term exposure to air pollution and COVID-19 hospitalization 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. 16

Figure S11: Effect modification[*] of the association between long-term exposure to air pollution and COVID-19 hospitalization among the 3,721,810 participants of the AIRCODEN cohort by co-morbidities at the cohort baseline on March 1, 2020. 17

Figure S12: Effect modification* of the association between long-term exposure to air pollution and COVID-19 mortality 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. 18

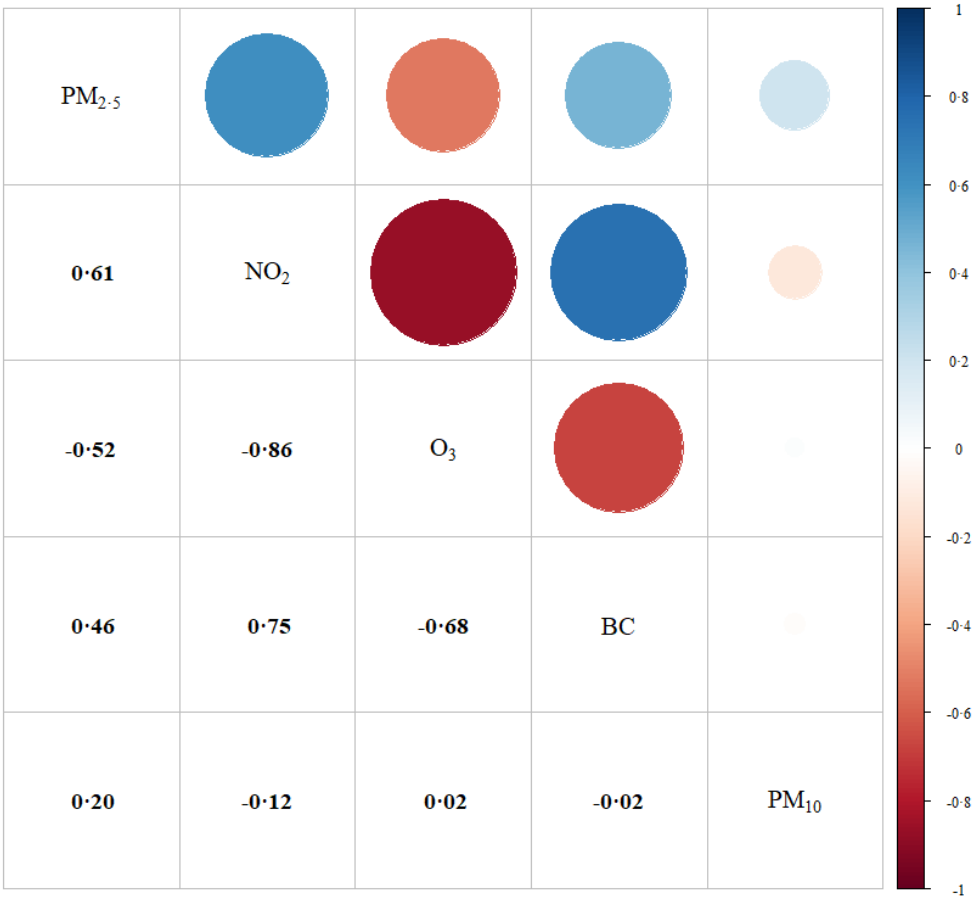
Figure S13: Effect modification* of the association between long-term exposure to air pollution and COVID-19 mortality among the 3,721,810 participants of the AIRCODEN cohort by co-morbidities at the cohort baseline on March 1, 2020. 19

Table S1: Definition and prevalence of co-morbidities among the 3,721,813 participants of the AIRCODEN cohort at the study baseline on March 1, 2020.

	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%)
ALRI	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%)**

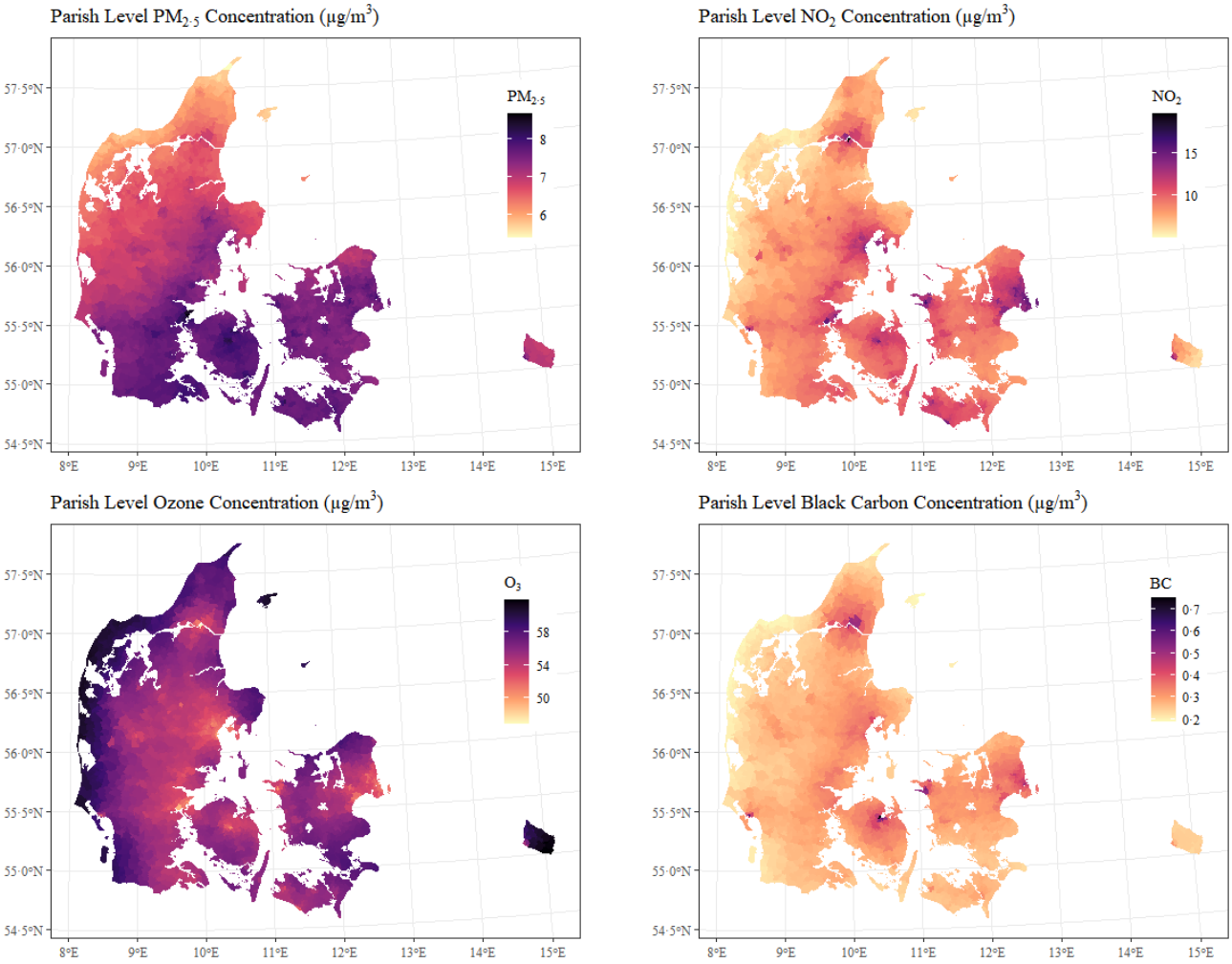
ICD-8/10: International Classification of Diseases 8th/10th version. ICD-8 was used before and ICD-10 after January 1, 1994 (ICD-9 was never implemented in Denmark). COPD=chronic obstructive pulmonary disease. ALRI=acute lower respiratory infection.

Figure S1: Pearson correlation coefficients between annual mean air pollution levels at residence in 2019 among the 3,721,813 participants of the AIRCODEN cohort.



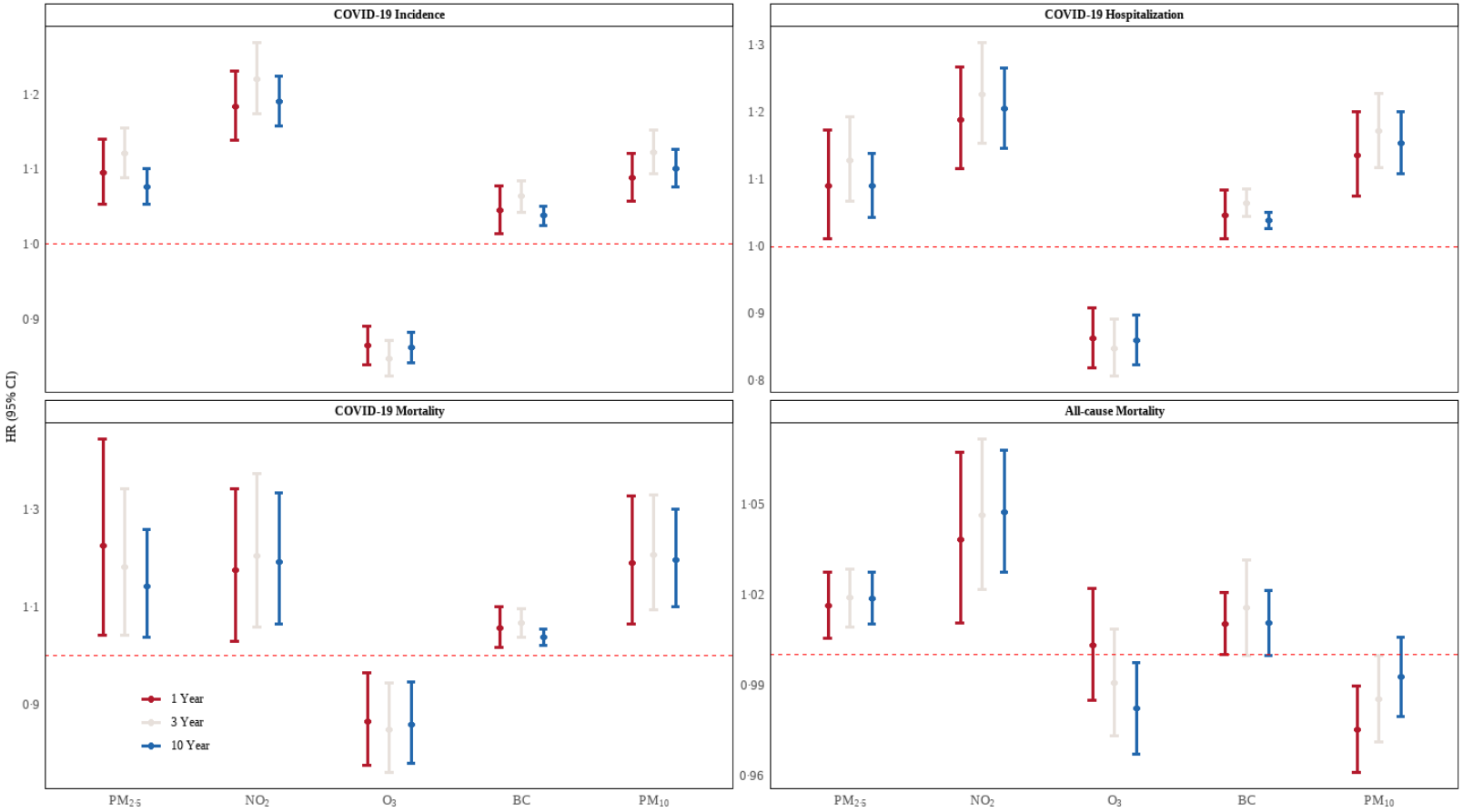
BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 µm, respectively.

Figure S2: Annual parish mean levels of $PM_{2.5}$, NO_2, BC and O_3 in 2019 in Denmark among the 3,721,813 participants of the AIRCODEN cohort.



BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 µm.

Figure S3: 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 different exposure windows of 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: 0.53 μg/m^3 for $PM_{2.5}$, 3.59 μg/m^3 for NO_2, 0.09 μg/m^3 for BC, 2.79 μg/m^3 for O_3, and 1.14 μg/m^3 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 health care. (analysis for all-cause mortality did not stratified by regions).

Table S2: The summary of the air pollution level estimated by DEHM/UBM model in 2019 and the ELAPSE model in 2010 among the 2,205,957 participants of the AIRCODEN cohort who had data on both exposures.

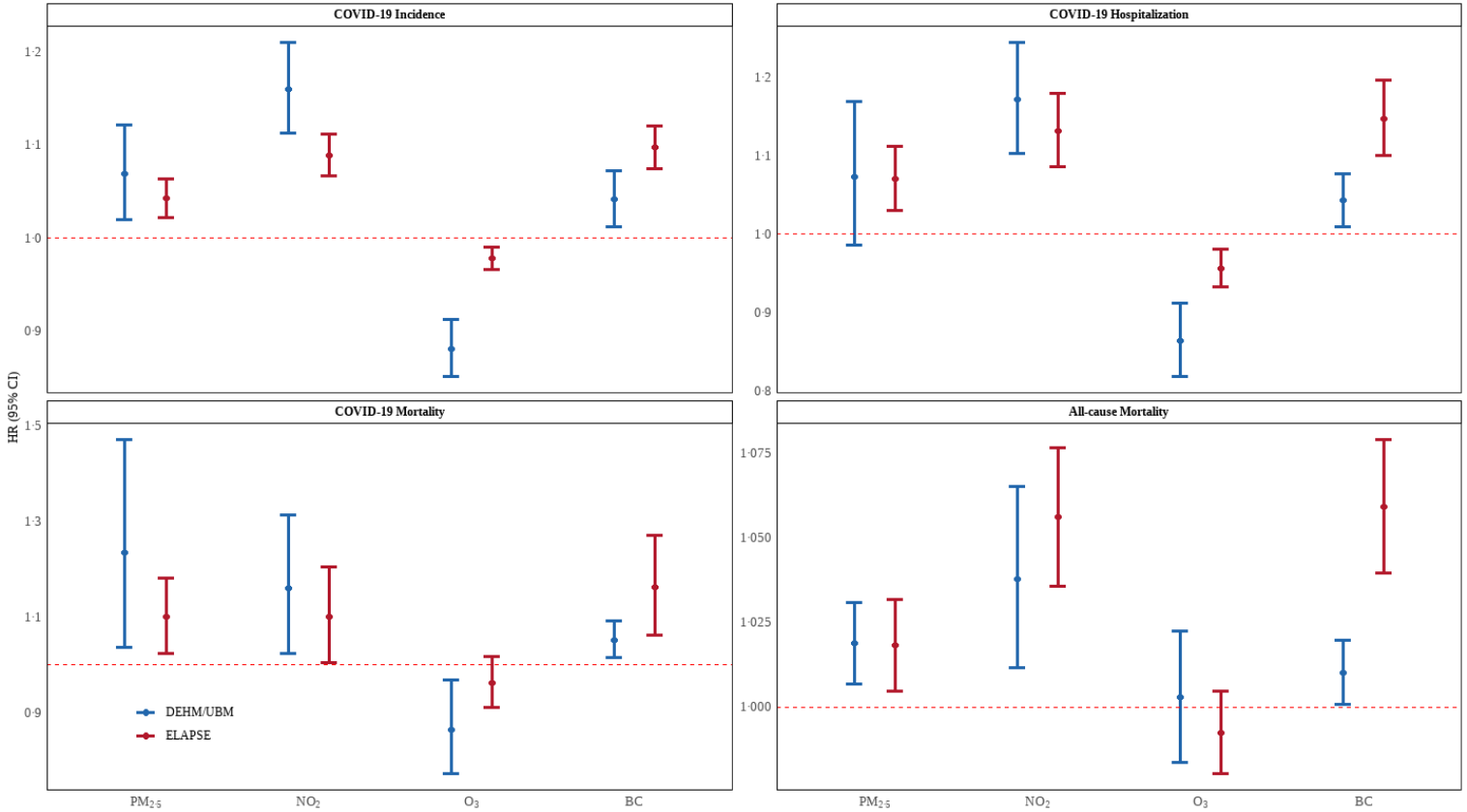
Air pollution	DEHM/UBM model		ELAPSE model	
	Mean±SD	IQR	Mean±SD	IQR
PM25	7.4±0.5	0.6	12.3±1.5	2.0
NO2	10.5±2.3	3.3	19.9±7.9	10.1
O3	54.7±2.2	2.9	80.4±4.3	4.1
BC	0.3±0.1	0.1	1.0±0.4	0.5

BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. $PM_{2.5}$=particulate matter with diameter $\leq$ 2.5 μm. SD=standard deviation, IQR=interquartile range. In ELAPSE model, O_3 was estimated during the warm season from April 1 to September 30 in 2010. In DEHM/UBM model, O_3 was estimated as the annual average concentration in 2019.

Figure S4: 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.

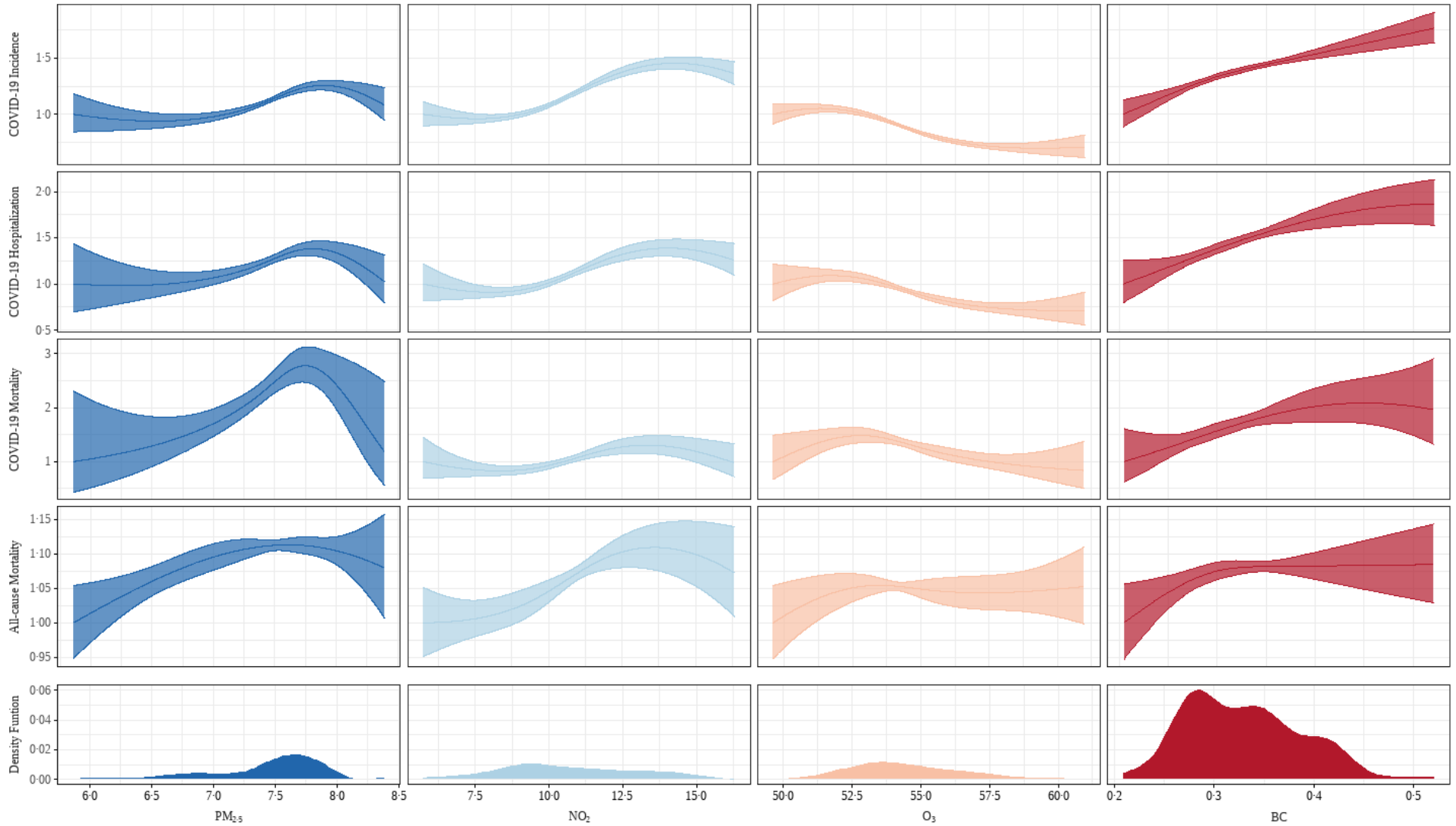
BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 µm, respectively. In ELAPSE model, O_3 was estimated during the warm season from April 1 to September 30 in 2010. In DEHM/UBM model, O_3 was estimated as the annual average concentration in 2019.

Figure S5: 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 two different exposure assessment models: DEHM/UBM model in 2019 and the ELAPSE model in 2010.



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 model-specific interquartile range increase: in DEHM/UBM 0.6 µg/m^3 for $PM_{2.5}$, 3.3 µg/m^3 for NO_2, 0.1 µg/m^3 for BC, and 2.9 µg/m^3 for O_3, and in ELAPSE 2.0 µg/m^3 for $PM_{2.5}$, 10.1 µg/m^3 for NO_2, 0.5 µg/m^3 for BC, and 4.1 µg/m^3 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 health care. (analysis for all-cause mortality did not stratified by regions). N for morbidity analysis: 2,205,956. 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 S6: 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. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 μm, respectively. All pollutants are in units $\mu g/m^3$. 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 health care. (analysis for all-cause mortality did not stratified by regions). All the plots are truncated to at 0.5% and 99.5% percentile for the corresponding exposures.

Table S3: The association between long-term exposure to air pollution and COVID-19 related morbidity and mortality below various cut-off values.

Pollutants	Cut-off levels	Number of participants	COVID-19 Incidence		COVID-19 Hospitalization		COVID-19 Mortality		All-cause Mortality	
			Number of events	HR (95%CI)	Number of events	HR (95%CI)	Number of events	HR (95%CI)	Number of events	HR (95%CI)
$PM_{2.5}$	All levels	3,721,813	138,742	1.10 (1.05-1.14)	11,270	1.09 (1.01-1.17)	2,557	1.23 (1.04-1.44)	62,359	1.02 (1.01-1.03)
	< 8 μg/m^3	3,521,340	132,801	1.13 (1.09-1.18)	10,839	1.14 (1.05-1.23)	2,490	1.32 (1.10-1.57)	58,905	1.02 (1.01-1.04)
	< 7.5 μg/m^3	1,641,307	51,678	1.13 (1.07-1.20)	4,172	1.25 (1.11-1.40)	950	1.51 (1.09-2.11)	27,526	1.03 (1.01-1.05)
	< 7 μg/m^3	677,418	16,409	1.04 (0.95-1.13)	1,263	1.19 (1.00-1.43)	296	1.74 (1.07-2.83)	11,640	1.04 (1.00-1.08)
NO_2	All levels	3,721,813	138,742	1.18 (1.14-1.23)	11,270	1.19 (1.12-1.27)	2,557	1.18 (1.03-1.34)	62,359	1.04 (1.01-1.07)
	< 15 μg/m^3	3,597,855	132,137	1.26 (1.21-1.31)	10,787	1.28 (1.19-1.38)	2,452	1.29 (1.10-1.51)	60,643	1.05 (1.02-1.09)
	< 13 μg/m^3	2,961,558	96,508	1.33 (1.25-1.41)	7,963	1.34 (1.20-1.50)	1,760	1.39 (1.12-1.73)	51,404	1.05 (1.01-1.08)
	< 10 μg/m^3	1,607,400	41,419	1.10 (1.00-1.21)	3,366	1.09 (0.89-1.33)	740	1.05 (0.68-1.61)	28,032	1.03 (0.97-1.09)
	< 8 μg/m^3	432,196	9,946	0.98 (0.76-1.25)	813	1.24 (0.68-2.28)	186	2.37 (0.68-8.28)	7,772	1.02 (0.90-1.17)
BC	All levels	3,721,813	138,742	1.05 (1.01-1.08)	11,270	1.05 (1.01-1.08)	2,557	1.06 (1.02-1.10)	62,359	1.01 (1.00-1.02)
	< 0.5 μg/m^3	3,685,856	137,343	1.20 (1.16-1.25)	11,159	1.20 (1.12-1.29)	2,541	1.25 (1.08-1.45)	61,834	1.02 (0.99-1.06)
	< 0.4 μg/m^3	3,196,323	111,021	1.25 (1.18-1.31)	9,250	1.29 (1.18-1.42)	2,123	1.38 (1.13-1.67)	55,368	1.05 (1.01-1.09)
	< 0.3 μg/m^3	1,355,757	34,675	1.14 (1.02-1.28)	2,964	1.36 (1.05-1.77)	643	1.93 (1.00-3.70)	24,515	1.05 (0.98-1.12)
O_3	All levels	3,721,813	138,742	0.86 (0.84-0.89)	11,270	0.86 (0.82-0.91)	2,557	0.87 (0.78-0.96)	62,359	1.00 (0.98-1.02)
	< 60 μg/m3	3,670,474	137,676	0.86 (0.84-0.89)	11,183	0.87 (0.82-0.92)	2,542	0.88 (0.79-0.99)	61,383	1.00 (0.98-1.02)
	< 56 μg/m3	2,869,443	115,939	0.88 (0.84-0.91)	9,236	0.88 (0.82-0.95)	2,084	0.96 (0.81-1.12)	46,452	1.00 (0.97-1.04)
	< 54 μg/m3	1,701,405	80,244	0.99 (0.95-1.05)	6,293	0.99 (0.90-1.09)	1,415	1.10 (0.88-1.39)	26,648	1.03 (0.98-1.09)
	< 52 μg/m^3	398,968	19,466	1.04 (0.96-1.12)	1,471	1.23 (0.96-1.58)	335	2.42 (1.25-4.68)	5,698	1.23 (1.10-1.37)

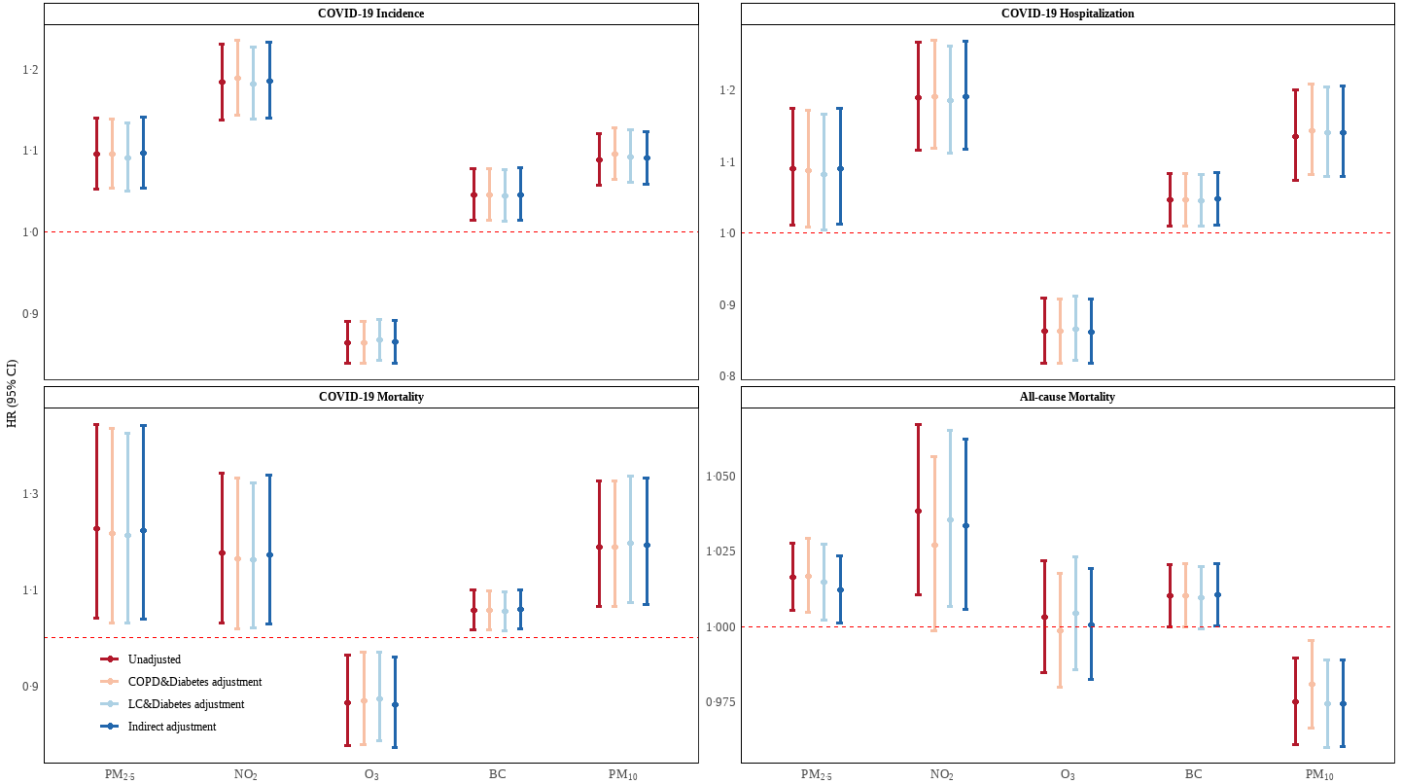
HR=hazard ratio. CI=confidence interval. BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 μm, respectively. Results are presented for interquartile range increase: 0.53 μg/m^3 for $PM_{2.5}$, 3.59 μg/m^3 for NO_2, 0.09 μg/m^3 for BC, 2.79 μg/m^3 for O_3, and 1.14 μg/m^3 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 health care. (analysis for all-cause mortality did not stratified by regions).

Table S4: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality among the 3,721,813 participants of the AIRCODEN cohort: two pollutant models.

Pollutants	Single-pollutant model	Two-pollutant model(Adjusted for pollutants below)				
		$PM_{2.5}$	NO_2	BC	O_3	PM_{10}
COVID-19 mortality (N=2,557)						
$PM_{2.5}$	1.23 (1.04-1.44)	/	1.16 (0.94-1.43)	1.21 (1.00-1.46)	1.14 (0.93-1.39)	1.14 (0.94-1.39)
NO_2	1.18 (1.03-1.34)	1.09 (0.92-1.29)	/	/	/	1.12 (0.97-1.29)
BC	1.06 (1.02-1.10)	1.02 (0.96-1.07)	/	/	1.03 (0.97-1.08)	1.03 (0.99-1.08)
O_3	0.87 (0.78-0.96)	0.91 (0.80-1.04)	/	0.88 (0.79-0.98)	/	0.89 (0.80-1.00)
PM_{10}	1.19 (1.07-1.33)	1.13 (0.99-1.31)	1.15 (1.02-1.30)	1.17 (1.05-1.31)	1.16 (1.03-1.30)	/
COVID-19 hospitalization (N=11,270)						
$PM_{2.5}$	1.09 (1.01-1.17)	/	0.97 (0.88-1.06)	1.05 (0.96-1.14)	0.94 (0.87-1.03)	1.02 (0.94-1.11)
NO_2	1.19 (1.12-1.27)	1.21 (1.12-1.30)	/	/	/	1.15 (1.08-1.23)
BC	1.05 (1.01-1.08)	1.04 (1.00-1.08)	/	/	1.01 (0.97-1.06)	1.03 (0.99-1.07)
O_3	0.86 (0.82-0.91)	0.84 (0.79-0.89)	/	0.87 (0.82-0.92)	/	0.88 (0.84-0.93)
PM_{10}	1.14 (1.07-1.20)	1.13 (1.06-1.20)	1.09 (1.03-1.16)	1.12 (1.06-1.19)	1.10 (1.04-1.17)	/
COVID-19 incidence (N=138,742)						
$PM_{2.5}$	1.10 (1.05-1.14)	/	0.98 (0.94-1.03)	1.06 (1.01-1.11)	0.96 (0.92-1.01)	1.06 (1.01-1.11)
NO_2	1.18 (1.14-1.23)	1.20 (1.14-1.25)	/	/	/	1.17 (1.12-1.22)
BC	1.05 (1.01-1.08)	1.03 (1.00-1.07)	/	/	1.02 (0.99-1.04)	1.03 (1.00-1.07)
O_3	0.86 (0.84-0.89)	0.85 (0.82-0.88)	/	0.87 (0.84-0.90)	/	0.87 (0.85-0.90)
PM_{10}	1.09 (1.06-1.12)	1.07 (1.03-1.10)	1.04 (1.01-1.07)	1.07 (1.04-1.10)	1.05 (1.02-1.09)	/

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: 0.53 $\mu g/m^3$ for $PM_{2.5}$, 3.59 $\mu g/m^3$ for NO_2, 0.09 $\mu g/m^3$ for BC, 2.79 $\mu g/m^3$ for O_3, and 1.14 $\mu g/m^3$ 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 health care. (analysis for all-cause mortality did not stratified by regions).

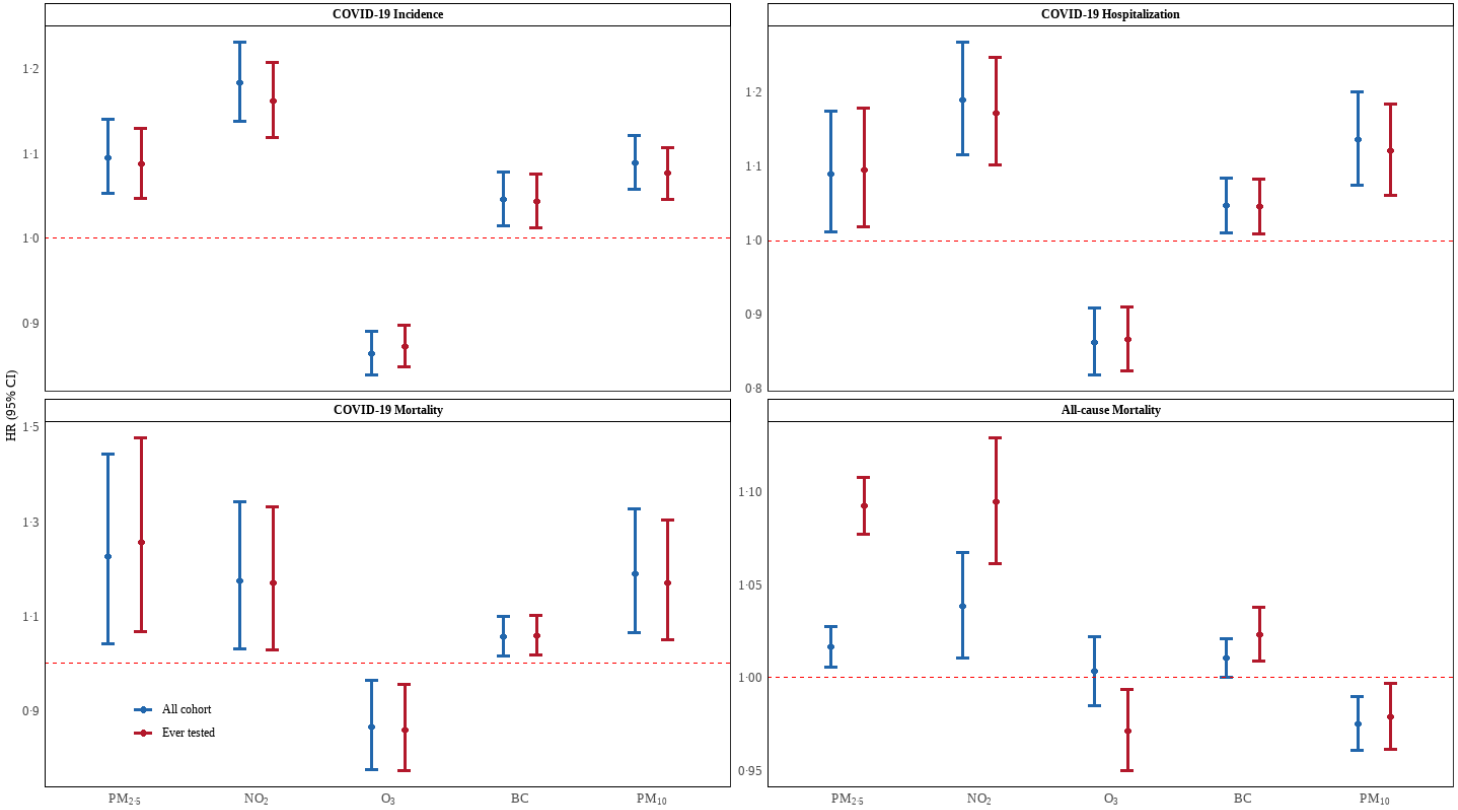
Figure S7: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the 3,721,813 participants of the AIRCODEN cohort with additional adjustment for missing information on individual lifestyle*.



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: 0.53 μg/m^3 for $PM_{2.5}$, 3.59 μg/m^3 for NO_2, 0.09 μg/m^3 for BC, 2.79 μg/m^3 for O_3, and 1.14 μg/m^3 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 health care. (analysis for all-cause mortality did not stratified by regions).

*COPD (smoking indicator), lung cancer (smoking indicator), and diabetes (BMI indicator) prevalence rates at parish-level. Indirect adjustment refers to Shin et al. methods for indirect adjustment for missing data on individual-levels of smoking and physical activity.

Figure S8: The association between long-term exposure to air pollution and COVID-19 incidence, hospitalization, and mortality, as well as all-cause mortality among the subset of 2,902,932 participants of the AIRCODEN cohort who were tested for COVID-19 (excluding 818,881 (22%) participants who were never tested for COVID-19 in the study period from March 1, 2020 until April 26, 2021).



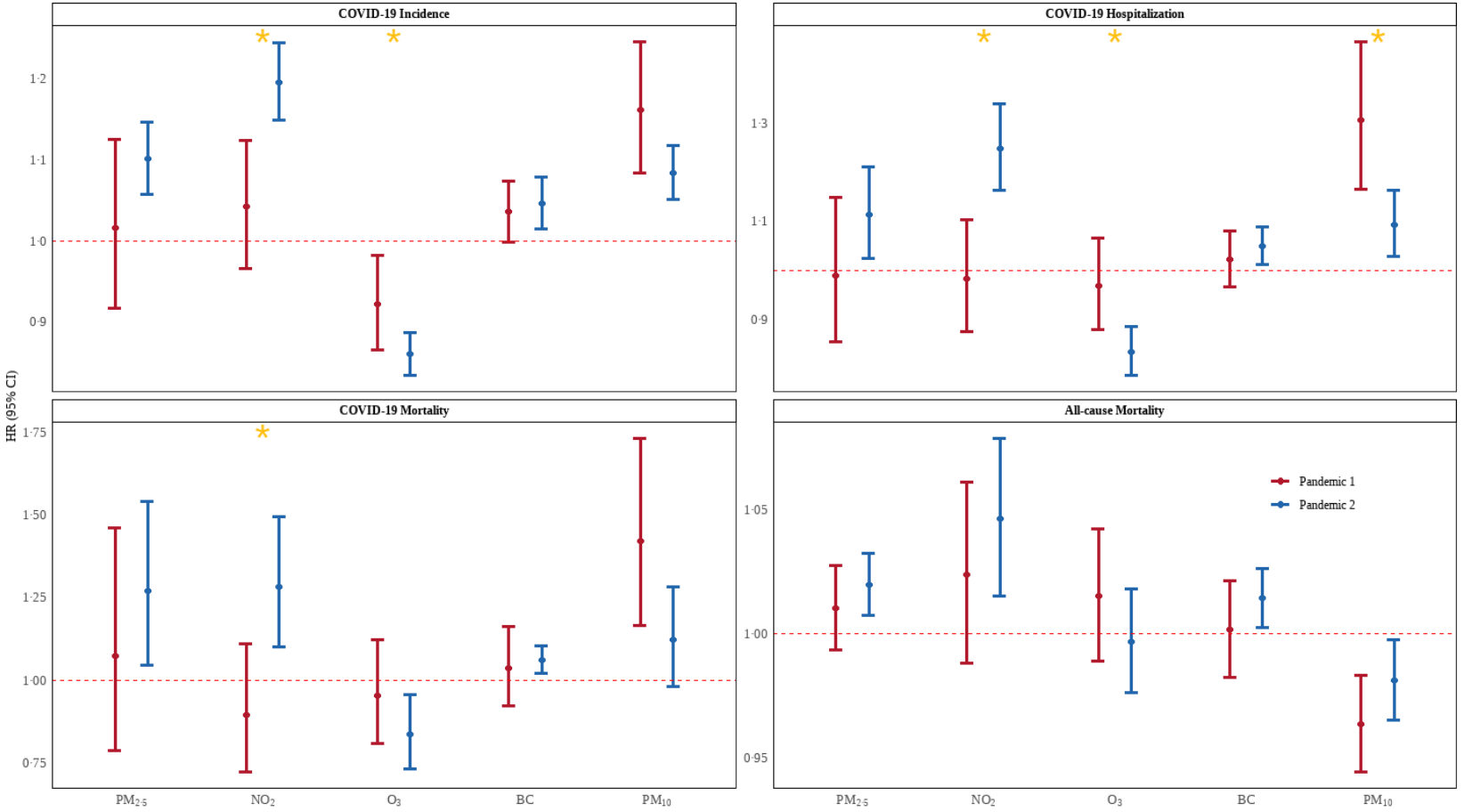
HR=hazard ratio. CI=confidence interval. BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 μm, respectively. Results are presented for interquartile range increase: 0.53 μg/m^3 for $PM_{2.5}$, 3.59 μg/m^3 for NO_2, 0.09 μg/m^3 for BC, 2.79 μg/m^3 for O_3, and 1.14 μg/m^3 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 health care. (analysis for all-cause mortality did not stratified by regions).

Table S5: The association between long-term exposure to air pollution and all-cause mortality as well as non-COVID-19 mortality among the 3,721,813 participants of the AIRCODEN cohort.

	Increase	All-cause Mortality (N=62,359)	Non-COVID-19 all-cause Mortality (N=59,802)
Per IQR			
$PM_{2.5}$	0.53	1.02 (1.01-1.03)	1.02 (1.01-1.03)
NO_2	3.59	1.04 (1.01-1.07)	1.03 (1.00-1.06)
BC	0.09	1.01 (1.00-1.02)	1.01 (1.00-1.02)
O_3	2.79	1.00 (0.98-1.02)	1.00 (0.98-1.02)
PM_{10}	1.14	0.98 (0.96-0.99)	0.99 (0.97-1.00)
Per fixed value			
$PM_{2.5}$	5	1.16 (1.05-1.28)	1.17 (1.06-1.29)
NO_2	10	1.11 (1.03-1.21)	1.09 (1.01-1.17)
BC	0.5	1.06 (1.00-1.12)	1.06 (1.00-1.12)
O_3	10	1.01 (0.95-1.08)	1.00 (0.94-1.07)
PM_{10}	10	0.80 (0.70-0.91)	0.88 (0.78-1.00)

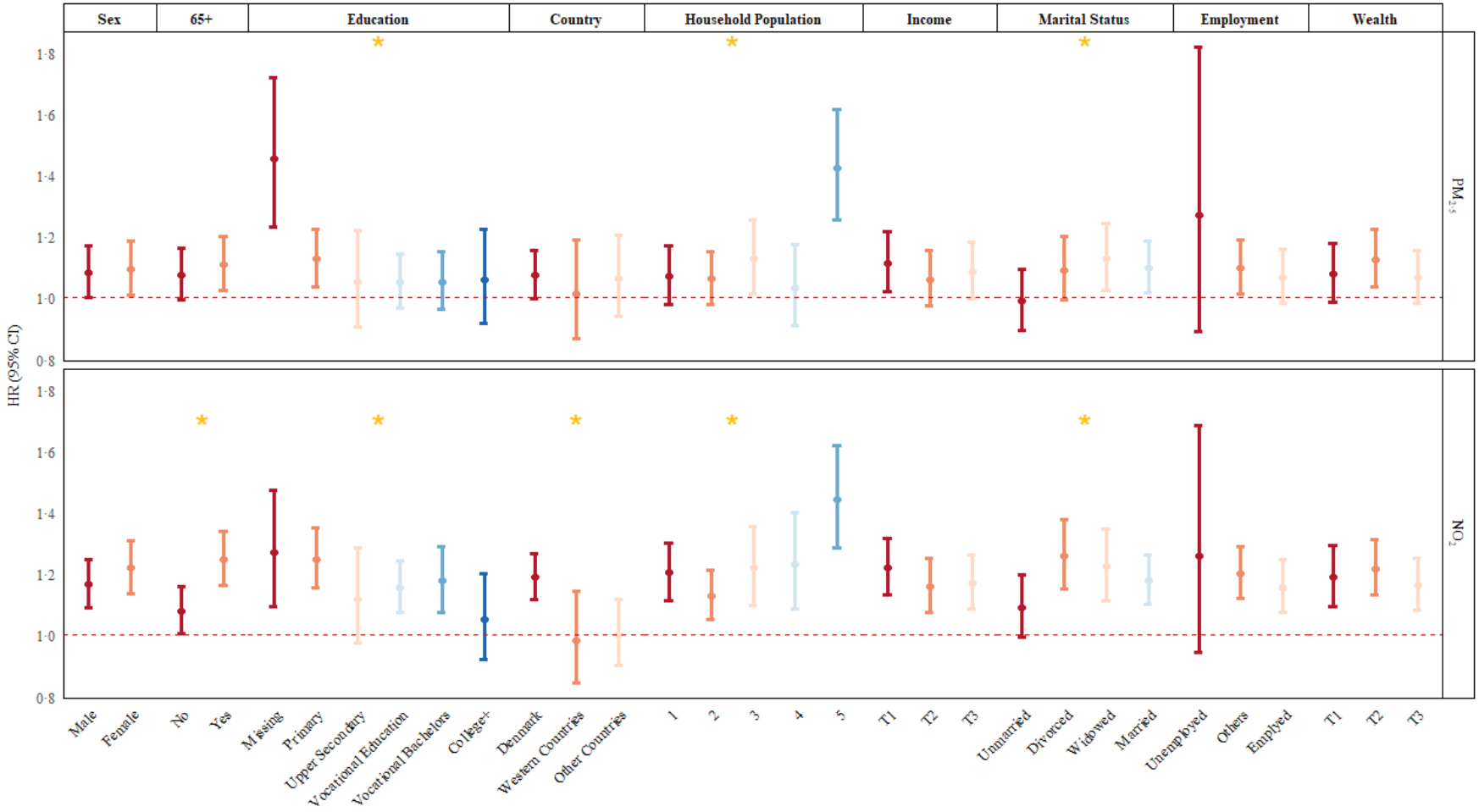
HR=hazard ratio. CI=confidence interval. BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 μm, respectively. Results are presented for interquartile range increase: 0.53 $\mu g/m^3$ for $PM_{2.5}$, 3.59 $\mu g/m^3$ for NO_2, 0.09 $\mu g/m^3$ for BC, 2.79 $\mu g/m^3$ for O_3, and 1.14 $\mu g/m^3$ for PM_{10}. Model adjusted for calendar time (time axis), sex (strata) , age at baseline (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 health care.

Figure S9: 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 in two pandemic waves: March 1-July 31, 2020 (red) and August 1, 2020-April 26, 2021 (blue).



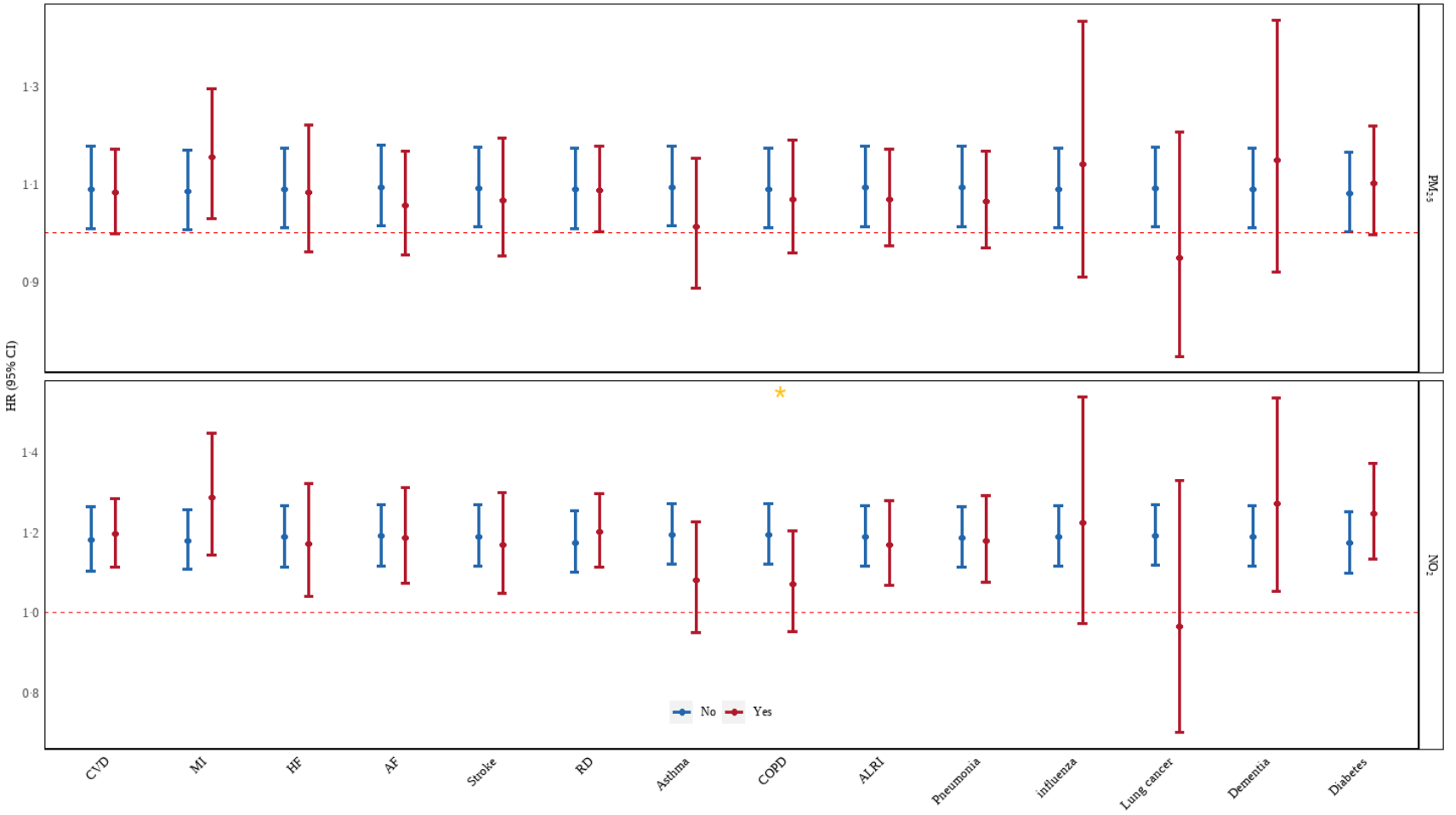
HR=hazard ratio. CI=confidence interval. BC= black carbon. NO_2=nitrogen dioxide. O_3 =ozone. PM_{10} and $PM_{2.5}$=particulate matter with diameter ≤ 10 and 2.5 µm, respectively. Results are presented for interquartile range increase: 0.53 µg/m^3 for $PM_{2.5}$, 3.59 µg/m^3 for NO_2, 0.09 µg/m^3 for BC, 2.79 µg/m^3 for O_3, and 1.14 µg/m^3 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); All-cause Mortality (P1=22,028, P2=40,331).

Figure S10: Effect modification* of the association between long-term exposure to air pollution and COVID-19 hospitalization 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.



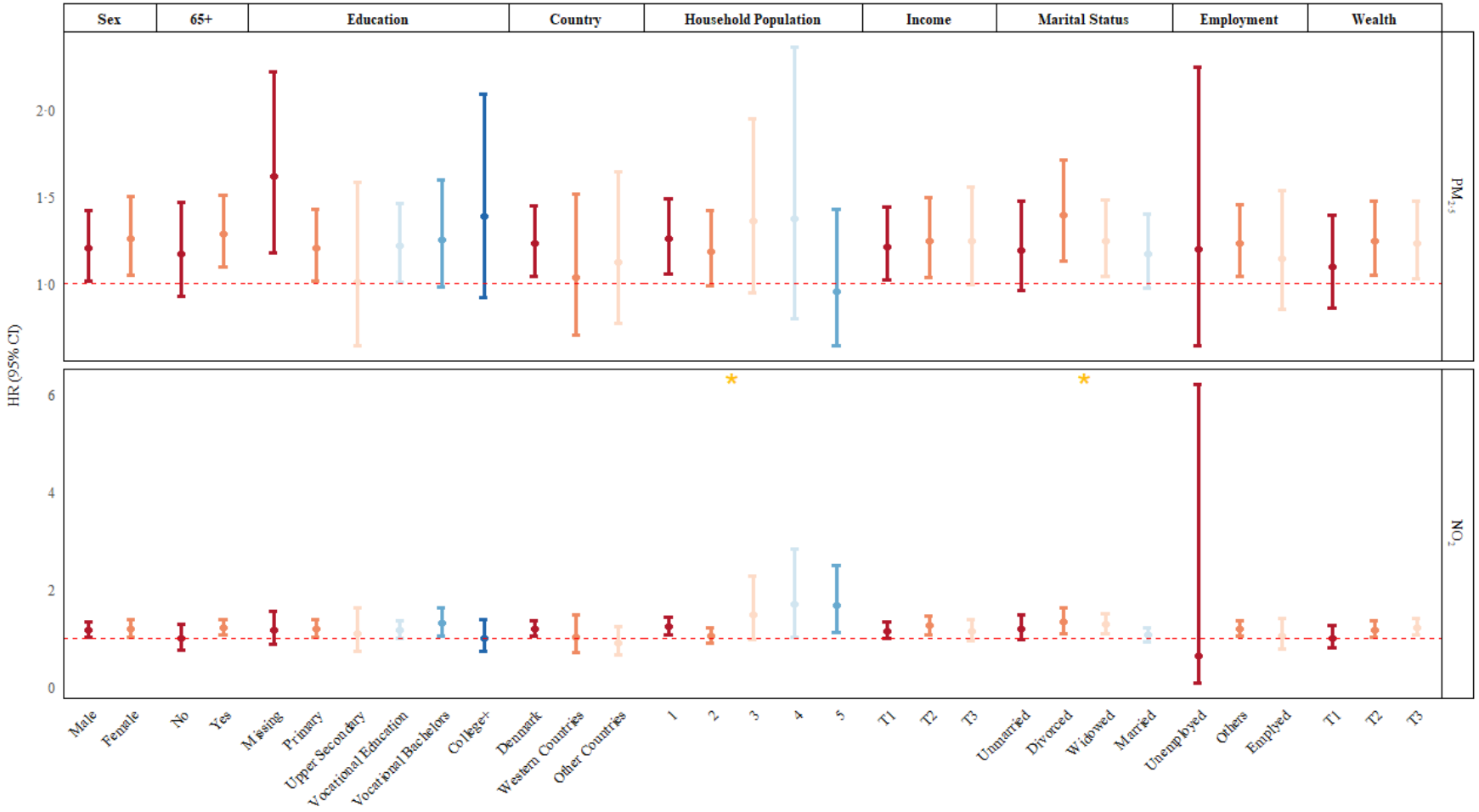
HR=hazard ratio. CI=confidence interval. NO_2=nitrogen dioxide. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 µm. Results are presented for interquartile range increase: 0.53 µg/m^3 for $PM_{2.5}$ and 3.59 µg/m^3 for NO_2.
*Wald test was used to calculate the global P-value, and results with P-value <0.05 are highlighted with a star.

Figure S11: Effect modification* of the association between long-term exposure to air pollution and COVID-19 hospitalization among the 3,721,810 participants of the AIRCODEN cohort by co-morbidities at the cohort baseline on March 1, 2020.



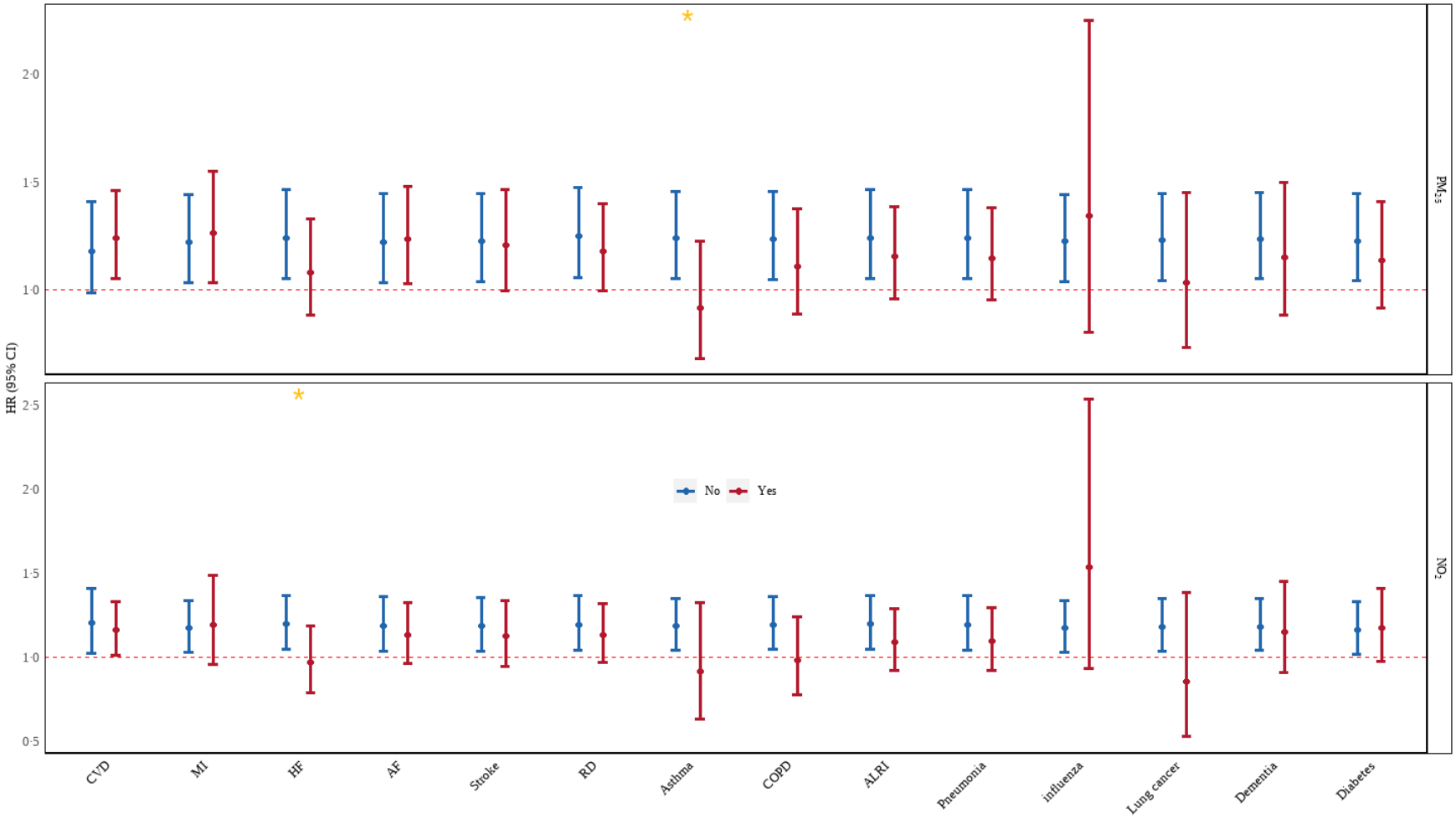
HR=hazard ratio. CI=confidence interval. NO_2=nitrogen dioxide. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 μm. CVD=cardiovascular disease. MI=myocardial infarction. HF=heart failure. AF=atrial fibrillation. RD=respiratory disease. COPD=chronic obstructive pulmonary disease. ALRI=acute lower respiratory infection. Results are presented for interquartile range increase: 0.53 $\mu g/m^3$ for $PM_{2.5}$ and 3.59 $\mu g/m^3$ 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 S12: Effect modification* of the association between long-term exposure to air pollution and COVID-19 mortality 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. $PM_{2.5}$=particulate matter with diameter ≤ 2.5 µm. Results are presented for interquartile range increase: 0.53 µg/m^3 for $PM_{2.5}$ and 3.59 µg/m^3 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 S13: Effect modification* of the association between long-term exposure to air pollution and COVID-19 mortality among the 3,721,810 participants of the AIRCODEN 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. CVD=cardiovascular disease. MI=myocardial infarction. HF=heart failure. AF=atrial fibrillation. RD=respiratory disease. COPD=chronic obstructive pulmonary disease. ALRI=acute lower respiratory infection. Results are presented for interquartile range increase: 0.53 $\mu g/m^3$ for $PM_{2.5}$ and 3.59 $\mu g/m^3$ 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.