



Air quality in Germany as a contributing factor to morbidity from COVID-19

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ABSTRACT

Background: The SARS-CoV-2 virus has been spreading in Germany since January 2020, with regional differences in incidence, morbidity, and mortality. Long-term exposure to air pollutants as nitrogen dioxide (NO₂), nitrogen monoxide (NO), ozone (O₃), and particulate matter (<10 µm PM₁₀, <2.5 µm PM_{2.5}) has a negative impact on respiratory functions. We analyze the association between long-term air pollution and the outcome of SARS-CoV-2 infections in Germany.

Methods: We conducted an observational study in Germany on county-level, investigating the association between long-term (2010–2019) air pollutant exposure (European Environment Agency, AirBase data set) and COVID-19 incidence, morbidity, and mortality rate during the first outbreak of SARS-CoV-2 (open source data Robert Koch Institute). We used negative binomial models, including adjustment for risk factors (age, sex, days since first COVID-19 case, population density, socio-economic and health parameters).

Results: After adjustment for risk factors in the tri-pollutant model (NO₂, O₃, PM_{2.5}) an increase of 1 µg/m³ NO₂ was associated with an increase of the need for intensive care due to COVID-19 by 4.2% (95% CI 1.011–1.074), and mechanical ventilation by 4.6% (95% CI 1.010–1.084). A tendency towards an association of NO₂ with COVID-19 incidence was indicated, as the results were just outside of the defined statistical significance (+1.6% (95% CI 1.000–1.032)). Long-term annual mean NO₂ level ranged from 4.6 µg/m³ to 32 µg/m³.

Conclusions: Our results indicate that long-term NO₂ exposure may have increased susceptibility for COVID-19 morbidity in Germany. The results demonstrate the need to reduce ambient air pollution to improve public health.

1. Trial registration number and date of registration

Not applicable.

2. Introduction

The COVID-19 pandemic continues to have severe implications for

societies around the world, with major impacts on the health care sector. Early during the pandemic, there was evidence that ambient air pollution can increase the vulnerability and susceptibility to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (Domingo et al., 2020). In general, ambient air pollution is a major environmental risk factor, related to acute and chronic respiratory diseases, lung cancer, stroke, and cardiovascular diseases (Environment Agency, 2020).

Abbreviations: ARDS, acute respiratory distress syndrome; CAMS, Copernicus Atmospheric Monitoring Service; CHD, coronary heart disease; COVID-19, Coronavirus Disease 2019; DIVI, German Interdisciplinary Association for Intensive Care and Emergency Medicine; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; SI, supplement information; NO₂: nitrogen dioxide, NO: nitrogen monoxide, O₃: ozone; PM_{2.5}: particulate matter <2.5 µm, PM₁₀: particulate matter <10 µm; 95% CI, 95% confidence interval.

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Long-term exposure to air pollutants can also increase the risk to develop acute respiratory distress syndrome (ARDS) (Rhee et al., 2019; Reilly et al., 2019).

Emerging in December 2019 in Wuhan, China, SARS-CoV-2 has spread around the globe. It has since affected more than 540 million people and caused 6.3 million deaths approximately two years after emergence (Hopkins University and Medicine, 2022). The development of ARDS associated to COVID-19 infection is the major cause for admission to intensive care units (ICU). Morbidity and mortality rate in COVID-19 diseases are also impacted by a variety of individual risk factors (e.g., age, sex, and chronic diseases such as hypertension, obesity, etc. (Williamson et al., 2020; Dorjee et al., 2020)), and/or low socio-economic status (Hsu et al., 2020)). To improve the reliability of statistical models on COVID-19, it is important to adjust for these risk factors (Villeneuve and Goldberg, 2020).

Since January 2020 many studies have analyzed the association between air pollution and COVID-19 incidence and mortality, however few studies focused on the severity of COVID-19 as a parameter, (e.g., the need for intensive care treatment or mechanical ventilation), or adjusted their model with risk factors, such as age, sex, population density, socio-economic status and/or health parameters (Marques et al., 2021).

Here we explore the impact of long-term ambient air pollution on the incidence, the need for ICU treatment, the need for mechanical ventilation, and the mortality caused by SARS-CoV-2 infections in Germany, based on data from the first COVID-19 outbreak in spring 2020.

3. Methods

We conducted an observational, county-based study normalized to population in Germany for the first COVID-19 outbreak, March–May 2020, to analyze the association between long-term (2009–2019) exposures of nitrogen dioxide (NO₂), nitric oxide (NO), ozone (O₃), and particulate matter (aerodynamic diameter <10 µm (PM₁₀), aerodynamic diameter <2.5 µm (PM_{2.5})) with COVID-19 cases, deaths, incidence, the numbers of occupied ICU beds, occupied mechanical ventilators on the ICU, and COVID-19 mortality.

Ethical approval was obtained from the ethical commission of the Charité (EA2/038/21; head: Prof. Dr. Kaschina). Patient consent was waived, because no individual patient data were collected and data analysis was performed anonymously.

3.1. Study area and COVID-19 situation in Germany

Since February 1, 2020, any suspected COVID-19 case had to be reported to the national health authorities, the Robert Koch Institute (RKI) (Koch Institute, 2022). Local public health departments at county level assessed COVID-19 cases and fatalities daily.

Test capacities increased fast within the first weeks and had a sufficient level since March and could be performed throughout Germany if needed. The first prominent COVID-19 case was announced January 27 by the RKI. On March 22 all federal states in Germany announced social distancing, prohibition of gatherings of more than 2 people, with the exception of household members and closure of schools and daycare facilities.

From April 1 the German Interdisciplinary Association for Intensive Care and Emergency Medicine (DIVI) implemented a registry for all ICU beds and mechanical ventilation capacities on ICUs within Germany (Koch Institut, 2022). The aim was to facilitate patient care in case of insufficient ICU bed capacities. Within the DIVI registry, each hospital reported how many COVID-19 patients needed ICU treatment and mechanical ventilation daily. As of April 16, reporting to the DIVI registry was mandatory for all German hospitals. Due to the centralized information sharing made possible by the DIVI registry, ICU and ventilator capacities never fell short during the outbreak in Germany in spring 2020.

The first outbreak of COVID-19 cases started in February 2020 and had the highest numbers of new COVID-19 infections registered in the week from March 16–March 23, with more than 3000 new cases reported daily. The highest number of COVID-19 patients needing ICU care were reported on April 18, with 2922 patients. Declining numbers of COVID-19 infections resulted in a cautious opening of playgrounds, zoos, and churches at the end of April 2020. Private gatherings with people from another household were allowed from May 6, schools reopened on May 4 and borders to surrounding countries were gradually reopened from May 15, 2020. Slight variations in reopening existed across states in Germany but were generally within a day or two of those dates given here.

3.1.1. COVID-19 data

COVID-19 cases, deaths, and first documented case (date) in each county were obtained from the open source database of the Robert Koch Institute (Koch Institute, 2022). We included COVID-19 cases and deaths from March 4, 2020, the date when the International Travel Trade Show in Berlin and the Leipzig book fair were canceled and private meetings were restricted to members of the own household, to avoid the influence of cluster events. Data were included up to May 16, after which lock down restriction began to be lifted. Incidence and mortality rate per 100,000 inhabitants were calculated at county level.

To sub-classify COVID-19 patients with a severe course of the illness, we extracted the number of occupied ICU beds and mechanical ventilators on the ICU from the DIVI registry (Koch Institut, 2022). The hospital-based reported data were allocated to the appropriate county in Germany. Data were included from April 16, the start of mandatory reporting, until May 16, when lock down restrictions were lifted. Data were calculated per 100,000 inhabitants. For additional information on data pre-processing see the supplemental material, Section S1.

3.1.2. Air pollution data

Long-term air pollution data were collected from 2010 through 2019. The preparation of the air pollution data to provide concentrations at the level of county are provided in detail in Caseiro et al. (2021) and described briefly below (Caseiro and von Schneidmesser, 2021).

Hourly concentrations of NO₂, NO, O₃, PM_{2.5}, and PM₁₀ at background stations were downloaded from Airbase (Environment Agency, 2021). Metrics, e.g., annual mean concentration, were calculated at the spatial level of county in Germany, corresponding to the Nomenclature of Territorial Unit for Statistics level 3 (NUTS-3). To gap-fill where air quality monitoring data was not available, a relationship between Copernicus Atmospheric Monitoring Service (CAMS) global reanalysis data (Inness et al., 2019) and the monitoring data was developed and used to estimate missing data. See Table 1 for federal state level averages or Caseiro et al. (2021) for access to the complete open-access dataset (Caseiro and von Schneidmesser, 2021). For the present study, the “average” scenario was chosen for the main analysis and the “remote” and “urban” scenarios were considered for sensitivity analyses.

3.1.3. Basic population data, socio-economic and health-related parameters

Population density, age (fraction of people older than 64) and sex (fraction of female) distribution were extracted from the open source database of the Federal Statistical Office of Germany (Bundesamt, 2021) on county level for the year 2019 (detailed description see supplement information (SI) Figure S1).

Socio-economic and health data were extracted from a representative epidemiological and health-monitoring survey (November 2014–July 2015; 24,016 subjects) conducted in Germany by the RKI (Sass et al., 2017). Extracted data included the fraction of people suffering hypertension, coronary heart disease (CHD), diabetes, asthma, chronic kidney disease, obesity (body mass index above 30), and daily smoking behavior. Furthermore, socio-economic parameters including the fraction of people born in non-EU states, people with low socio-economic status, and school attendance of 10 years or less were

Table 1

Descriptive statistics at State level in Germany (covering 392 counties) for COVID-19 disease parameters and air pollution. Disease parameters are per 100,000 residents, given as medians. Values in parentheses are the 25th and 75th percentiles. Long-term air pollution concentrations from 2010 through 2019, inclusive, are provided as mean $\pm$ standard deviation with the minimum and maximum values in parentheses. These values reflect the mean and the standard deviation, and in parentheses percentiles 25 and 75, of the decadal means for individual counties within each state.

Federal state	County data			COVID-19 disease parameter				Long-Term Air Pollutants 2010 - 2019				
	Counties (n)	Population (n)	First Case (Date)	Incidence 04.03.-16.05.20	Mortality 04.03.-16.05.20	Days on ICU 16.04.-16.05.20	Days with ventilation on ICU 16.04.-16.05.20	Annual mean NO2 ($\mu\text{g}/\text{m}^3$)	Annual mean NO ($\mu\text{g}/\text{m}^3$)	O3 daily 8h max ($\mu\text{g}/\text{m}^3$)	Annual mean PM2.5 ($\mu\text{g}/\text{m}^3$)	Annual mean PM10 ($\mu\text{g}/\text{m}^3$)
Baden-Württemberg	42	10,867,995	03.01.20	660 (461/1110)	37 (19/62)	82 (60/118)	59 (39/85)	19.7 $\pm$ 3.8 (6.5/28.9)	11.1 $\pm$ 3.2 (3.1/21.1)	164.9 $\pm$ 5.1 (155.4/177)	12.8 $\pm$ 1.32 (6.5/13.9)	17.4 $\pm$ 1.4 (11.5/19.2)
Bavaria	91	12,637,769	02.01.20	346 (226/500)	17 (8/30)	72 (36/178)	52 (25/116)	18.6 $\pm$ 3.5 (8.6/30.0)	9.8 $\pm$ 3.0 (1.7/29.1)	161.3 $\pm$ 2.9 (151.1/168)	12.9 $\pm$ 0.6 (10/14.2)	17.4 $\pm$ 1.4 (10.1/20.8)
Berlin	1	3,669,491	01.01.20	176	6	105	85	20.0	10.7	162.6	16.7	21.2
Brandenburg	17	2,422,215	06.01.20	168 (67/357)	6 (2/20)	21 (7/48)	15 (5/28)	13.9 $\pm$ 3.5 (4.7/17.7)	6.9 $\pm$ 3.2 (0.6/14.8)	159.3 $\pm$ 3.1 (152.5/162.5)	13.9 $\pm$ 1.4 (11.2/16.3)	18.3 $\pm$ 1.8 (14.3/20.8)
Bremen	2	681,202	26.02.20	627 (83/627)	23 (5/23)	79 (50/79)	47 (35/58)	21.8 $\pm$ 0.4 (21.5/22.1)	6.5 $\pm$ 0.1 (6.4/6.6)	153.1 $\pm$ 0.3 (152.9/153.3)	13.4 $\pm$ 0.3 (13.3/13.6)	18.6 $\pm$ 0.0 (18.6/18.6)
Hamburg	1	1,847,253	17.01.20	270	14	120	98	23.5	14.2	151.5	14.1	20.2
Hessen	26	6,288,080	01.01.20	306 (221/395)	14 (5/24)	68 (38/119)	49 (23/91)	18.2 $\pm$ 6.1 (7.9/32)	9.6 $\pm$ 5.3 (1.3/20.9)	166.3 $\pm$ 6 (154.5/181.2)	13.2 $\pm$ 0.5 (11.5/13.8)	17.0 $\pm$ 2.5 (10.6/20.8)
Mecklenburg-West Pomerania	8	1,608,138	28.02.20	80 (78/120)	2 (2/3)	4 (17/89)	1 (0/16)	10.5 $\pm$ 4.4 (5.7/16.5)	3.3 $\pm$ 3.1 (0.8/8.3)	156.3 $\pm$ 4.8 (149.8/162.5)	12.6 $\pm$ 0.5 (12/13)	17.3 $\pm$ 1.4 (14.7/18.4)
Lower Saxony	45	7,667,567	01.01.20	160 (105/301)	8 (3/17)	24 (7/67)	11 (2/39)	15.6 $\pm$ 3.0 (7.2/19.5)	7.6 $\pm$ 2.1 (1/9.8)	161.2 $\pm$ 3.9 (147.2/171.8)	12.6 $\pm$ 0.8 (9.8/13.6)	16.8 $\pm$ 1.2 (11.7/18.6)
North Rhine-Westphalia	53	17,947,221	01.01.20	601 (400/814)	23 (13/39)	68 (36/93)	43 (27/72)	21.9 $\pm$ 4.5 (10.8/31.8)	15.2 $\pm$ 5. (8.7/36.8)	166.1 $\pm$ 6.2 (160.4/180.1)	14.0 $\pm$ 1.3 (11.5/17.7)	19.5 $\pm$ 0.3 (15.7/24.1)
Rhineland-Palatinate	35	3,939,294	21.01.20	155 (101/223)	5 (2/10)	17 (4/89)	10 (0/51)	17.1 $\pm$ 5.5 (6.7/30.6)	10.5 $\pm$ 4.8 (3.0/23.1)	164.0 $\pm$ 4.6 (153.9/172.6)	12.9 $\pm$ 1.1 (8.3/14.3)	16.9 $\pm$ 2.1 (11.6/19.9)
Saarland	6	986,887	31.01.20	279 (191/690)	12 (4/46)	55 (27/128)	29 (10/50)	17.7 $\pm$ 2.5 (15.6/22.3)	9.5 $\pm$ 1.5 (6.8/10.9)	163.3 $\pm$ 2.8 (160.2/167.3)	13.1 $\pm$ 0.5 (12.4/13.7)	17.6 $\pm$ 0.7 (16.5/18.8)
Saxony	13	4,071,971	01.01.20	362 (217/567)	12 (5/22)	34 (10/70)	21 (7/32)	16.4 $\pm$ 3.8 (10.1/21.2)	8.0 $\pm$ 4.1 (2.8/15.9)	161.3 $\pm$ 3.9 (155/167.7)	13.5 $\pm$ 1.0 (11/14.6)	17.8 $\pm$ 2.5 (12.4/20.9)
Saxony-Anhalt	14	2,194,782	22.02.20	109 (66/156)	3 (2/7)	21 (7/40)	7 (3/25)	15.8 $\pm$ 3.3 (9.9/19.4)	7.4 $\pm$ 2.5 (3.1/11.2)	161.1 $\pm$ 3.4 (153.8/168.5)	13.7 $\pm$ 1.2 (11.7/15.7)	18.1 $\pm$ 1.2 (15.8/20.2)
Schleswig-Holstein	15	2,903,772	05.01.20	169 (83/281)	4 (3/15)	31 (5/40)	19 (3/29)	14.7 $\pm$ 3.4 (6.1/21)	7.7 $\pm$ 2.3 (1.0/12.4)	153.0 $\pm$ 7.7 (141.7/162.7)	12.6 $\pm$ 0.8 (10.8/13.7)	16.9 $\pm$ 1.3 (13.7/19.7)
Thuringia	23	2,133,378	21.01.20	98 (60/151)	3 (2/12)	21 (9/125)	21 (5/85)	15.7 $\pm$ 4.5 (4.6/21.4)	9.7 $\pm$ 3.7 (0.6/18.7)	159.0 $\pm$ 3.3 (152.5/163.8)	12.6 $\pm$ 1.2 (8.0/13.8)	16.9 $\pm$ 2.4 (10.9/20.0)
All Counties	392	81,967,016	01.01.-28.02.2020	176 (112/272)	7 (3/15)	57 (26/107)	39 (14/74)	17.8 $\pm$ 4.7 (4.6/32.0)	10.0 $\pm$ 4.5 (0.6/36.8)	162.2 $\pm$ 5.3 (141.7/181.2)	13.1 $\pm$ 1.1 (6.5/17.7)	17.6 $\pm$ 1.9 (10.1/24.1)

also extracted. These data points were only available at the state level.

Age range, sex, socio-economic and health data were included based on identified risk factors for a severe COVID-19 course, as in published systematic reviews focusing on that subject (Williamson et al., 2020; Dorjee et al., 2020).

3.2. Statistics

From 402 counties within Germany, we included 392 counties in our analysis, 10 counties were excluded due to no DIVI data (no reporting hospitals).

We calculated negative binominal models to estimate the association between long-term air pollutant exposure and COVID-19 parameters. We fit single-pollutant and tri-pollutant models to estimate the effect of each pollutant without and with control for co-pollutants. Since we found high correlations between NO_2 and NO (Pearson Correlation 0.879, p -value < 0.001) and between PM_{10} and $\text{PM}_{2.5}$ (Pearson Correlation 0.621, p -value < 0.001) we performed a tri-pollutant model including NO_2 , O_3 and $\text{PM}_{2.5}$ to avoid collinearity.

We adjusted our models by the following parameters: days since first COVID-19 case, age >64 years, sex distribution, and population density. In the next step, we adjusted our models for the potential health and socio-economic confounders.

To improve the validity of our model we conducted a number of sensitivity analyses, including limiting the analysis to include only counties with modelled air quality data below 20% (i.e. measured data representing over 80%), different periods for incidence and mortality analysis (from January 1 until May 16, 2020; from April 16 until May 16, 2020), and case fatality rate.

We did not adjust for test capacity or availability of health care services, since shortages in these areas was not an issue in Germany (ALM-Akkreditierte Labore in der Medizin, 2021).

We did not perform zero-inflated negative binominal models since

we had no zeros in COVID-19 cases and only 19 zeros in COVID-19 deaths per county. We had no zeros in ICU beds occupied and 17 zeros for required mechanical ventilation.

Results of the negative binomial models are presented as main effect estimates with 95% confidence intervals. For the count component, the results indicate the change in percentage of COVID-19 cases, deaths, incidence, occupied ICU beds, required mechanical ventilation in ICU and COVID-19 mortality also with a 95% confidence interval. Calculations were performed with SPSS, Version 26 (Copyright IBM, Inc., Chicago, IL 60606, USA).

4. Results

In 392 counties in Germany from March 4 - May 16, 2020, there were 169,840 COVID-19 cases and 8433 deaths. COVID-19 parameters and long-term air pollution data are given in Table 1 and Figs. 1 and 2.

All results discussed here are those for COVID-19 parameters per 100,000 inhabitants. For model results based on counts, see SI, Tables S4 – S9. In the tri-pollutant model (NO_2 , O_3 , $\text{PM}_{2.5}$) adjusted to basic population data and all confounders (Table 2), we found a $1 \mu\text{g}/\text{m}^3$ increase in NO_2 was significantly associated with an increase in occupied ICU beds by 4.2% (95% CI 1.011–1.074) and the need for mechanical ventilation by 4.6% (95% CI 1.010–1.084). In the same tri-pollutant model but with PM_{10} rather than $\text{PM}_{2.5}$, a $1 \mu\text{g}/\text{m}^3$ increase in NO_2 was associated with an increased risk for all COVID-19 parameters (incidence, ICU beds, ICU ventilation, mortality), ranging from 2.8% to 6.6% (see SI, Table S9). The positive association of NO_2 and an increased risk for needing an ICU bed and mechanical ventilation (see SI, Tables S1 – S9) was persistent throughout all models, including the single pollutant models, indicating a robust result.

The model results adjusted to basic population data but without adjustment to confounders also indicate a strong association between NO_2 and all COVID-19 parameters (a $1 \mu\text{g}/\text{m}^3$ increase in NO_2 resulted in

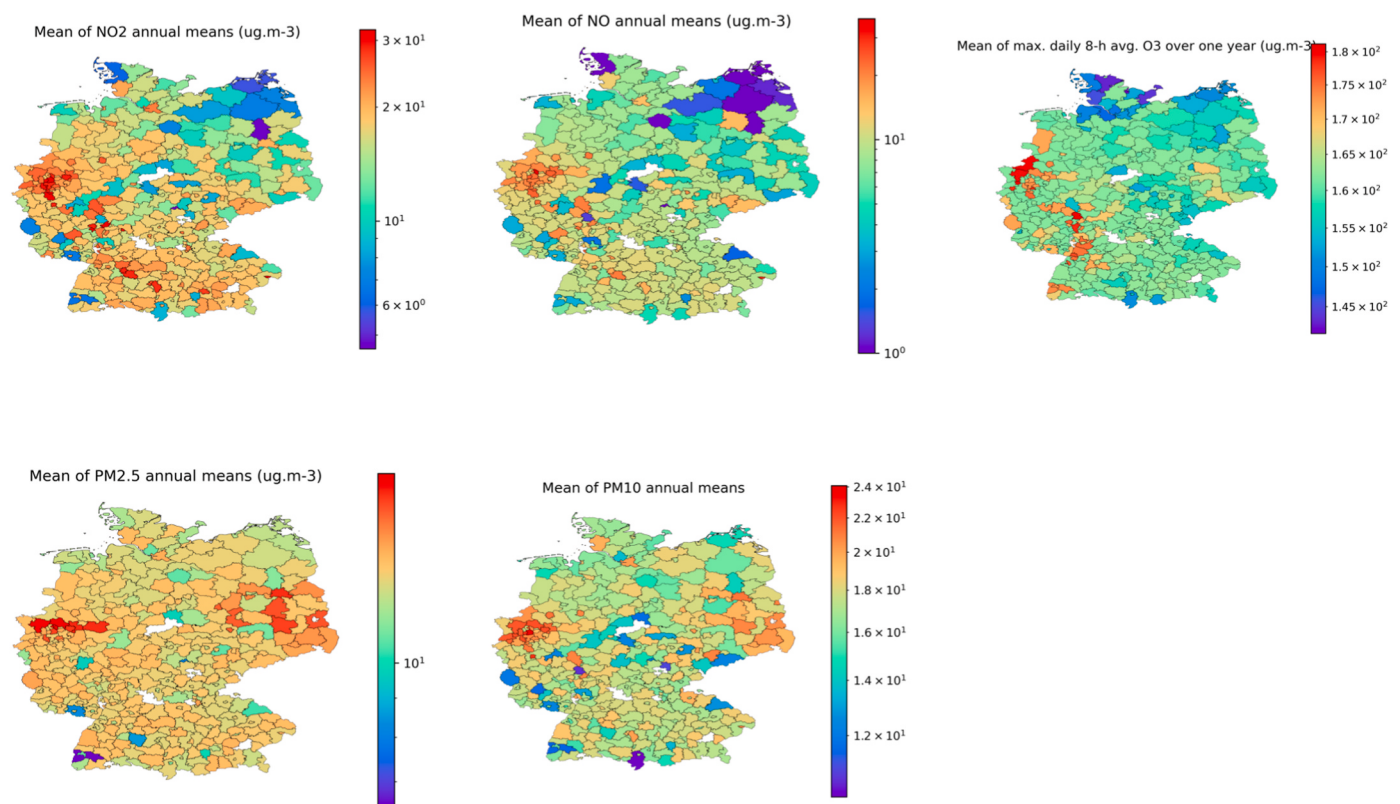


Fig. 1. Title: Air pollution metrics for 2010 through 2019, **Legend:** The plots show air pollution metrics that are averaged across all 10 years by county on a log scale.

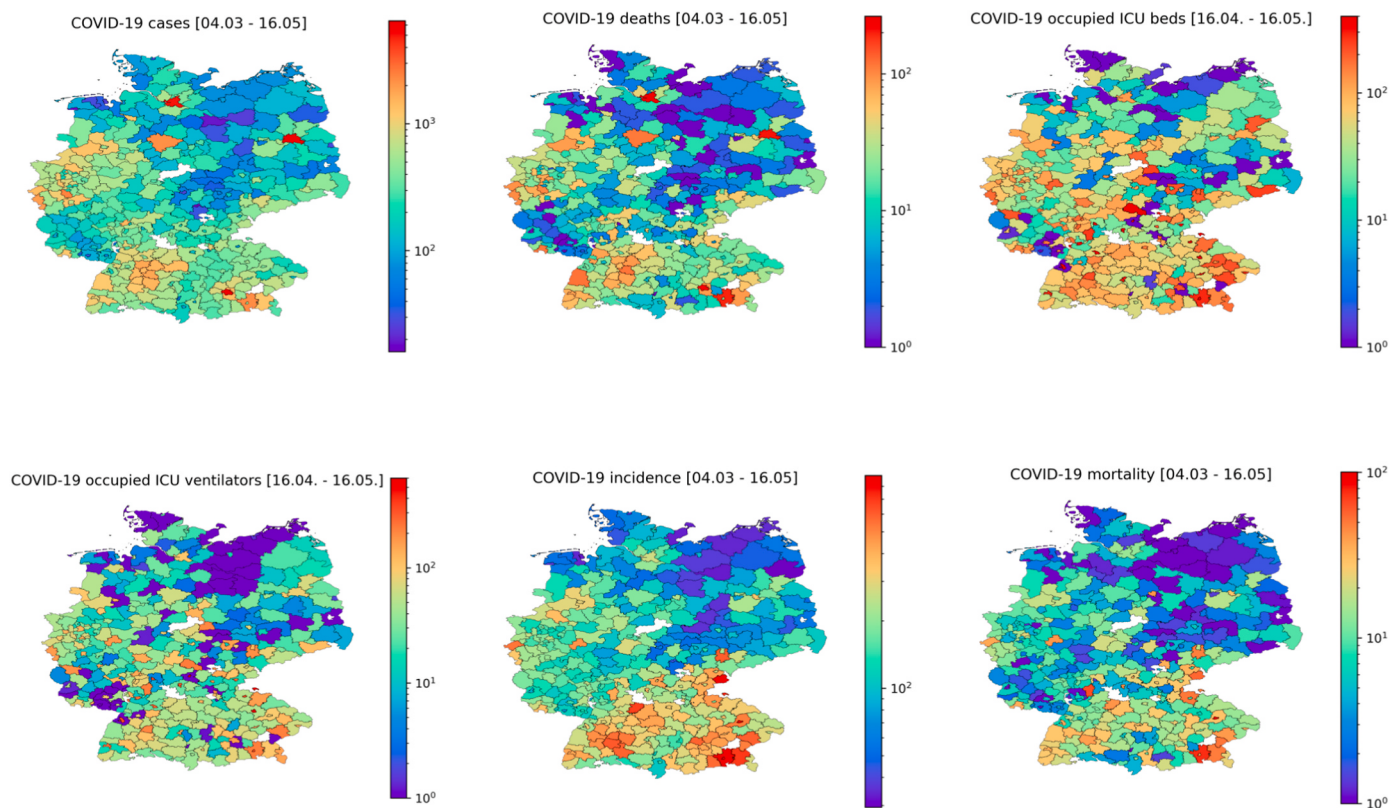


Fig. 2. Title: COVID-19 parameters in numbers and per 100,000 residents by county, Legend: COVID-19 parameters in numbers and per 100,000 residents by county evaluated in the models for the dates given above on a log scale. For counties that were reporting but had e.g., no deaths, a zero is shown. The counties that are white had no hospitals reporting DIVI data and were therefore left out of the analysis.

increased risks ranging from 4.7% to 10.3% in the tri-pollutant models (see SI, Tables S5, S8) and from 3.4% to 4.6% in the single pollutant models (see SI, Table S2)).

The only pollutants other than NO₂ to show a significant association to the COVID-19 parameters in the single pollutant models were NO (incidence, ICU beds, and ICU ventilation) and to a more limited extent O₃ (incidence) (see SI, Table S1). However, after adjustment to basic population data only NO had a significant positive association to incidence, ICU beds, and ICU ventilation (see SI, Table S2), and after adjustment to all confounders none of the associations to NO and O₃ remained significant (see SI, Table S3).

For comparability with previous studies (see discussion section) we calculated models with no adjustments for number of inhabitants (counts only). These models show similar results, typically with stronger associations.

Sensitivity analyses were performed that evaluated alternative air pollution metrics (urban or remote), COVID-19 parameters, and time scales, but this did not change the results in a meaningful way (see SI, Tables S10 – S14).

5. Discussion

In our county-level, observational study, we identified associations between long-term air pollution and COVID-19 disease parameters in Germany in spring 2020. Throughout all models, long-term NO₂ exposure had the most persistent impact on all COVID-19 disease parameters. After adjustment for all risk factors, our tri-pollutant model (including NO₂, O₃, and PM_{2.5}) showed that a 1 µg/m³ increase in annual mean NO₂ concentration was associated with an increase in ICU beds occupancy owing to COVID-19 by 4.2% (95% CI 1.011–1.074), and mechanical ventilation in the ICU by 4.6% (95% CI 1.010–1.084); incidence and mortality also had increased odds ratios, but not statistically significant.

5.1. Models including confounders

Studies adjusting for demographic, meteorological, socio-economic and health related factors found a positive association between long-term PM_{2.5} exposure and COVID-19 mortality during spring 2020 in the USA (Wu et al., 2020) and with COVID-19 cases, hospital admissions, and deaths in the Netherlands (Cole et al., 2020). A study analyzing the impact of long-term exposure (2014–2019) to NO₂, O₃, PM₁₀ and PM_{2.5} on COVID-19 mortality for each pollutant individually during spring and winter 2020 in California, USA also found positive associations for all included pollutants (Garcia et al., 2022). Studies correlating multi-pollutant exposure with COVID-19 disease parameters in England and the USA found that NO₂ was the main contributor to increased numbers of COVID-19 deaths and mortality rate (Travaglio et al., 2021; Liang et al., 2020), while they did not find an association between PM_{2.5} and O₃ and COVID-19 mortality (Travaglio et al., 2021; Liang et al., 2020). However, in the study by Travaglio et al. from England, COVID-19 cases were also positively associated with PM_{2.5} (Travaglio et al., 2021). An increase of 1 µg/m³ NO₂ was associated with 3.3% more cases and 3.1% more deaths in England (Travaglio et al., 2021) and an increase of 8.6 µg/m³ NO₂ was associated with 11.3% higher case-fatality rate and a 16.2% higher mortality rate in the United States. These results are in line with our tri-pollutant model including demographic, socio-economic and health related risk factors. Furthermore, we showed that an increase of 1 µg/m³ NO₂ increased COVID-19 morbidity, specifically the need for ICU beds (+4.2%) and the need for mechanical ventilation (+4.6%).

In a global exposure setup analyzing the impact of PM_{2.5} on COVID-19 mortality based on epidemiological data from the USA and China, it was estimated that PM_{2.5} contributes to ~15% to COVID-19 mortality worldwide, and to ~19% in Europe, where 70–80% of the anthropogenic fraction from the air pollution are attributed to fossil fuel combustion (Pozzer et al., 2020). Other pollutants were not quantified.

Table 2

Tri-Pollutant Model (NO₂, O₃ and PM_{2.5}) for the COVID-19 disease parameters after adjusting for basic county data (population density (people/km²), sex (% female), age (% 65 years and older), first case (days from first COVID-19 case until start of analysis)) and socio-economic and health data at federal state level (low socio-economic status (%), maximal 10 years school attendance (%), non-EU born (%), Hypertonia (%), coronary heart disease (%), diabetes mellitus (%), asthma (%), chronic kidney disease (%), BMI ≥30 (%), daily smoking (%)). All parameters were investigated for 04.03. – May 16, 2020, except those noted with an asterisk, which cover 16.04. – May 16, 2020. Results listed in red are considered significant based on the confidence interval. Exp (B) is the exponentiation of the B coefficient, which is an odds ratio.

COVID-19 parameters per 100,000 inhabitants	Air pollutant metric	Exp (B)	95% Confidence Interval	p-value
COVID-19 incidence	NO ₂ annual mean	1.016	1.000–1.032	0.055
	O ₃ daily 8h max	0.997	0.987–1.008	0.623
	PM _{2.5} annual mean	0.984	0.931–1.039	0.555
ICU beds*	NO ₂ annual mean	1.042	1.011–1.074	0.008
	O ₃ daily 8h max	0.993	0.973–1.012	0.462
	PM _{2.5} annual mean	0.914	0.820–1.018	0.102
ICU ventilation*	NO ₂ annual mean	1.046	1.010–1.084	0.013
	O ₃ daily 8h max	0.997	0.975–1.020	0.824
	PM _{2.5} annual mean	0.906	0.797–1.031	0.134
COVID-19 mortality	NO ₂ annual mean	1.027	0.996–1.060	0.088
	O ₃ daily 8h max	0.988	0.968–1.009	0.258
	PM _{2.5} annual mean	0.936	0.843–1.040	0.217

5.2. Models without adjustment to confounders

A number of studies calculated correlations between e.g., COVID-19 mortality and air pollutants (Ogen, 2020; Fattorini and Regoli, 2020). For example, a study by Ogen analyzed the correlation between COVID-19 mortality and NO₂ concentrations retrieved from satellites during the first outbreak in 2020 for 66 administrative regions in Italy, Spain, France, and Germany. A high correlation between NO₂ and mortality was found, specifically 83% of all deaths (which included in total 3701 fatalities by March 19th 2020) occurred in NO₂ hot spot regions where the maximum concentration was above 100 µmol/m² (Ogen, 2020). Such studies are relevant indicators for the potential impact air pollution may play in the context of respiratory pandemics. As noted in these studies, their conclusions should be used to motivate more in-depth research where a greater number of factors can be incorporated, such as we have here. For example, such a study from Italy that looked at the impact of long-term exposure (2016–2019) to different air pollutants (NO₂, PM_{2.5}, PM₁₀, and O₃) on COVID-19 cases found significant positive correlations with all air pollutants (Fattorini and Regoli, 2020). This is similar to our single pollutant model with no adjustment to number of inhabitants or confounders results where both COVID-19 cases and deaths were positively associated with almost all pollutants (Table S2). However, once the models are adjusted for population data and other confounders, many of these associations are no longer significant.

5.3. Air quality and pathophysiology

Despite the somewhat different results, all studies found a link between COVID-19 disease parameters and exposure to long-term ambient air pollutants (Marquès and Domingo, 2022). Since the beginning of

industrialization, ambient air pollution, caused by fossil fuel combustion for e.g., energy production and transport, as well as industrial agriculture, is an omnipresent hazard for human beings all around the world (Environment Agency, 2020). Children, pregnant women, older people, and those with comorbidities are most susceptible to air pollutants (Environment Agency, 2020). In Germany ca. 80,000 premature deaths per year are attributed to air pollution (Lelieveld, 2017). Recently, the World Health Organization (WHO) tightened the air quality guidelines, now recommending that the annual mean level of 5 µg/m³ for PM_{2.5} and 15 µg/m³ for PM₁₀ not be exceeded. Ground level O₃ should not exceed an 8-h daily maximum of 100 µg/m³ and annual mean NO₂ should not exceed 10 µg/m³ (World Health Organization, 2021). Of the 402 counties in Germany, only 6.9% and 7.7% of counties met the recommended limit for NO₂ and PM₁₀, respectively, but none met the recommended limit for O₃ and PM_{2.5} (see SI, Section 4).

Exposure to air pollutants causes oxidative stress, endothelial dysfunction, thrombogenicity and systemic inflammation, being associated with elevated levels of interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α, and C-reactive protein leading to an increase in cardiovascular and respiratory diseases (Lederer et al., 2021). Oxidative stress on the level of the epithelial lining fluid of the lungs occurs when inhaling air pollutants (Lakey et al., 2016). Inflammation is in part regulated by the renin-angiotensin system based on a feedback loop including the two main effectors Angiotensin II and Angiotensin 1-7 (Cantero-Navarro et al., 2021). The biological effects of both effectors are contrary, since Angiotensin II promotes vasoconstriction, cell growth, fibrosis, and increases inflammation and oxidative stress while Angiotensin 1-7 does the opposite – vasodilation, decreasing inflammation and oxidative stress and inhibiting cell growth (Forrester et al., 2018; Santos et al., 2018). A critical step in the transformation of Angiotensin II into Angiotensin 1-7 and thereby regulating systemic inflammation is run by the Angiotensin-converting-enzyme 2 (ACE-2) (Pucci et al., 2020). Importantly, the SARS-CoV-2 spike protein binds directly to the ACE-2 receptor to enter the cells (Wang et al., 2020; Zhang et al., 2020), reducing ACE-2 expression and worsening systemic inflammation (Kuba et al., 2005). ACE-2 has a protective role in ARDS by downregulating Angiotensin II and mitigating pro-inflammatory effects. In animal studies, it has been shown that exposure to air pollutants decreases Angiotensin 1-7 and ACE-2, thereby increasing Angiotensin-II (Du et al., 2020). The picture that emerges here is an imbalance of the renin-angiotensin system, over-activating the Angiotensin-II /inflammation side by SARS-CoV-2 and air pollution, which may be the underlying pathophysiology for all the above reviewed studies, providing an explanation for the positive association between exposure to ambient air pollution and COVID-19 incidence, morbidity, and mortality rates.

5.4. Limitations

Since our study was an observational study normalized to population, impact at the individual level from pre-existing diseases or behavioral differences following the pandemic lock-down restrictions are not included, which could result in bias. Moreover, we calculate an association between air pollutants and COVID-19 disease parameters, which does not guarantee causal relations.

The health and socio-economic confounders included in our model were only available at federal state level and not on county level. This could have minimized the associations in our results from the models including adjustment to all confounders.

Our study was conducted in Germany, with the respective composition in socio-economic status of the population, a relatively high-level health care system with sufficient capacity and overall good accessibility, and with substantial COVID-19 restrictions that were implemented, hence our results are not generalizable to all countries.

In general, the course of COVID-19 is influenced substantially by individual risk profiles; however, some of these risk factors are also

triggered by chronic exposure to air pollution, such as cardiovascular diseases, diabetes, acute respiratory dysfunction syndrome, COPD, and ischemic heart disease (Rhee et al., 2019; Lelieveld, 2017; Brook et al., 2004; Bowe et al., 2018). Because of this connection, there may be a bias in our models that underestimate the impact of air pollution on health during the COVID-19 pandemic.

6. Conclusion

Our results add another piece to the puzzle, demonstrating the impact of air pollution in the COVID-19 pandemic. They show that the risk to need ICU treatment and mechanical ventilation after COVID-19 infection is influenced by individual, long-term exposure to NO₂. While the COVID-19 pandemic may end by reaching herd immunity through infection or vaccination, exposure to ambient air pollution will continue to affect the health of people, with a focus on NO₂ in Germany. The only remedy is reducing emissions. Since the main source for outdoor NO₂ are motor vehicles, a transition to clean transportation in Germany is urgently needed. This will improve air quality, help mitigate climate change and improve population health and quality of life.

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board of the Charité (EA2/038/21), head Prof. Dr. Med. Kaschina. Patient consent was waived, because no individual patient data were collected and data analysis was performed anonymously.

Consent for publication

Not applicable.

Availability of data and material: The Air Pollution Data are available at: APEXpose.DE dataset in the form of an ASCII file: APEXpose.DE_2010–2019.csv. DOI: <https://doi.org/10.1038/s41597-021-01068-6>. See Caseiro et al. (2021) for all further information associated to the generation of the dataset. Population data were open source data from the Robert Koch Institute https://www.rki.de/EN/Content/Health_Monitoring/Public_Use_Files/public_use_file_node.html; <https://www.intensivregister.de/#/inde>; and from the Federal Statistical Office of Germany at <https://www-genesis.destatis.de/genesis/online>.

Code availability

Software code for negative binomial model analysis are located in the supplement material (SPSS code).

Authors contributions

Susanne Koch: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, roles/writing – original draft, Writing – review & editing. Christina Hoffmann: Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. Alexandre Caseiro: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. Marie Ledebur: Data curation, Resources, Software, Supervision, Validation, Writing – review & editing. Mario Menk: Data curation, Methodology, Supervision, Writing – review & editing. Erika von Schneidmesser: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, roles/writing – original draft, Writing – review & editing.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.envres.2022.113896>.

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