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

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Research Article

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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 (NO_2), nitrogen monoxide (NO), ozone (O_3), and particulate matter (<10µm PM_{10}, < 2.5µm $PM_{2.5}$,) 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 a cross-sectional study in Germany on county-level, investigating the association between long-term (2010-2019) air pollutant exposure and COVID-19 incidence, morbidity, and mortality rate during the first outbreak of SARS-CoV-2. We used negative binominal 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 (NO_2, O_3, $PM_{2.5}$) an increase of 1µg/m³ NO_2 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 NO_2 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 NO_2 level ranged from 4.6µg/m³ to 32µg/m³.

Conclusions: Our results indicate that long-term NO_2 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.

Trial registration number and date of registration: not applicable

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) [1]. In general, ambient air pollution is a major environmental risk factor, related to acute and chronic respiratory diseases, lung cancer, stroke, and cardiovascular diseases [2]. Long-term exposure to air pollutants can also increase the risk to develop acute respiratory distress syndrome (ARDS) [3, 4].

Emerging in December 2019 in Wuhan, China, SARS-CoV-2 has spread around the globe. It has since affected more than 364 million people and caused 5.6 million deaths approximately two years after emergence [5]. 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. [6, 7], and/or low socio-economic status [8]). To improve the reliability of statistical models on COVID-19, it is important to adjust for these risk factors [9].

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 [10].

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.

Methods

We conducted a cross-sectional, county-based study in Germany for the first COVID-19 outbreak, March – May 2020, to analyze the association between long-term (2009 – 2019) exposures of nitrogen dioxide (NO_2), nitric oxide (NO), ozone (O_3), and particulate matter (aerodynamic diameter <10 µm (PM_{10}), 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.

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). 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. However, retrospectively, it was noted that many COVID-19 cases had occurred as early as January 1, 2020. On March 4th major events with more than 1,000 participants were forbidden. 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. 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 on March 1, 2020 and had the highest numbers of new COVID-19 infections registered in the week from March 30 – April 3, with more than 30,000 new cases reported daily. The highest number of COVID-19 patients needing ICU care were reported on April 18, with 2,928 patients. Declining numbers of COVID-19 infections resulted in a cautious opening of playgrounds, zoos, and churches on April 30. Private gatherings with people from another household were allowed from May 6, schools reopened on May 11 and borders to surrounding countries were gradually reopened from May 13, 2020. Slight variations in reopening existed across states in Germany but were generally within a day or two of those dates given here.

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 [11]. We included COVID-19 cases and deaths from March 4, 2020, the time point after which large events were prohibited 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 [12]. 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.

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 [13].

Hourly concentrations of NO_2, NO, O_3, $PM_{2.5}$, and PM_{10} at background stations were downloaded from Airbase [14]. 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). An averaging strategy which favours more remote stations was used when more than one station was present in the county. To gap-fill where air quality monitoring data was not available, a relationship between Copernicus Atmospheric Monitoring Service (CAMS) global reanalysis data [15] 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 [13].

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 [16] 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 [17]. 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 also extracted. These data points were only available at the state level.

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 $PM_{2.5}$ (Pearson Correlation 0.621, p-value < 0.001) we performed a tri-pollutant model including NO_2, O_3 and $PM_{2.5}$ 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 [18].

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).

Results

In 392 counties in Germany from March 4 - May 16, 2020, there were 169,840 COVID-19 cases and 8,433 deaths. COVID-19 parameters and long-term air pollution data are given in Table 1 and Figure 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, $PM_{2.5}$) adjusted to basic population data and all confounders (Table 2), we found a 1 µg/m³ 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 $PM_{2.5}$, a 1 µg/m³ 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.

Table 2

Tri-Pollutant Model (NO_2, O_3 and $PM_{2.5}$) for the COVID-19 disease parameters after adjusting for basic county data (population density (people/km^2), 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 $\geq$ 30 (%), daily smoking (%)). All parameters were investigated for 04.03. – 16.05.2020, except those noted with an asterisk, which cover 16.04. – 16.05.2020. 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

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 µg/m^3 increase in NO_2 resulted in increased risks ranging from 4.7% - 10.3% in the tri-pollutant models (see SI, Tables S5, S8) and from 3.4% - 4.6% in the single pollutant models (see SI, Table S2)).

The only pollutants other than NO_2 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 O_3 (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 O_3 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, COVID-19 parameters, and time scales, but this did not change the results in a meaningful way (see SI, Tables S10 – S14).

Discussion

In our county-level, cross-sectional study, we identified associations between long-term air pollution and COVID-19 disease parameters in Germany in spring 2020. Throughout all models, long-term NO_2 exposure had the most persistent impact on all COVID-19 disease parameters. After adjustment for all risk factors, our tri-pollutant model (including NO_2, O_3, and $PM_{2.5}$) showed that a 1 µg/m³ increase in annual mean NO_2 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.

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 [19] and with COVID-19 cases, hospital admissions, and deaths in the Netherlands [20]. A study analyzing the impact of long-term exposure (2014-2019) to NO_2, O_3, PM_{10} 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 [21]. Studies correlating multi-pollutant exposure with COVID-19 disease parameters in England and the USA found that NO_2 was the main contributor to increased numbers of COVID-19 deaths and mortality rate [22, 23], while they did not find an association between $PM_{2.5}$ and O_3 and COVID-19 mortality [22, 23]. However, in the study by Travaglio et al. from England, COVID-19 cases were also positively

associated with $PM_{2.5}$ [22]. An increase of 1 µg/m³ NO_2 was associated with 3.3% more cases and 3.1% more deaths in England [22] and an increase of 8.6 µg/m^3 NO_2 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 NO_2 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 [24]. Other pollutants were not quantified.

Models without adjustment to confounders

A number of studies calculated correlations between e.g., COVID-19 mortality and air pollutants [25, 26]. For example, a study by Ogen analyzed the correlation between COVID-19 mortality and NO_2 concentrations retrieved from satellites during the first outbreak in 2020 for 66 administrative regions in Italy, Spain, France, and Germany. A high correlation between NO_2 and mortality was found, specifically 83% of all deaths (which included in total 3,701 fatalities by March 19th 2020) occurred in NO_2 hot spot regions where the maximum concentration was above 100 µmol/m^2 [25]. 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 (NO_2, $PM_{2.5}$, PM_{10}, and O_3) on COVID-19 cases found significant positive correlations with all air pollutants [26]. 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.

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. 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 [2]. Children, pregnant women, older people, and those with comorbidities are most susceptible to air pollutants [2]. In Germany ca. 80,000 premature deaths per year are attributed to air pollution [27]. 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 PM_{10} not be exceeded. Ground level O_3 should not exceed an 8-hour daily maximum of 100 µg/m³ and annual mean NO_2 should not exceed 10 µg/m³ [28]. Of the 402 counties in Germany, only 6.9% and 7.7% of counties met the recommended limit for NO_2 and PM_{10}, respectively, but none met the recommended limit for O_3 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-a, and C-reactive protein leading to an increase in cardiovascular and respiratory diseases [29]. Oxidative stress on the level of the epithelial lining fluid of the lungs occurs when inhaling air pollutants [30]. 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 [31]. 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 [32, 33]. 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) [34]. Importantly, the SARS-CoV-2 spike protein binds directly to the ACE-2 receptor to enter the cells [35, 36], reducing ACE-2 expression and worsening systemic inflammation [37]. 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 [38]. 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.

Limitations

Since our study has a cross-sectional, epidemiological design, 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.

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 [3, 27, 39, 40]. 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.

Conclusion

Our results add another piece to the puzzle, demonstrating the impact of air pollution in the COVID-19 pandemic. It shows that the risk for COVID-19 infection, the need of ICU treatment and mechanical ventilation is influenced by individual, long-term exposure to air pollutants. 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. The only remedy is reducing emissions. The transition to renewable energy, clean transportation, and sustainable agriculture is urgently needed to improve air quality, which will also help mitigate climate change, to improve population health and quality of life around the world.

Abbrevations

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, NO_2: nitrogen dioxide, NO: nitrogen monoxide, O_3: ozone, $PM_{2.5}$: particulate matter < 2.5µm, PM_{10}: particulate matter < 10µm, 95% CI: 95% confidence interval

Declarations

Ethics approval and consent to participate:

Ethic 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. 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 binominal model analysis are located in the supplement material (SPSS code).

Conflicts of interest/Competing interests:

The authors declare to have no conflict of interests or competing interests.

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Authors' contributions:

Principal investigator: SK, EvS; Conceived and designed the experiments SK, CH, EvS; Data preprocessing was done by AC, ML, MM. Analyzed the data: SK, CH, AC, EvS. Wrote and reviewed the manuscript: SK, CH, AC, ML, MM, EvS.

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Table

Table 1 is available in the Supplementary Files section

Figures

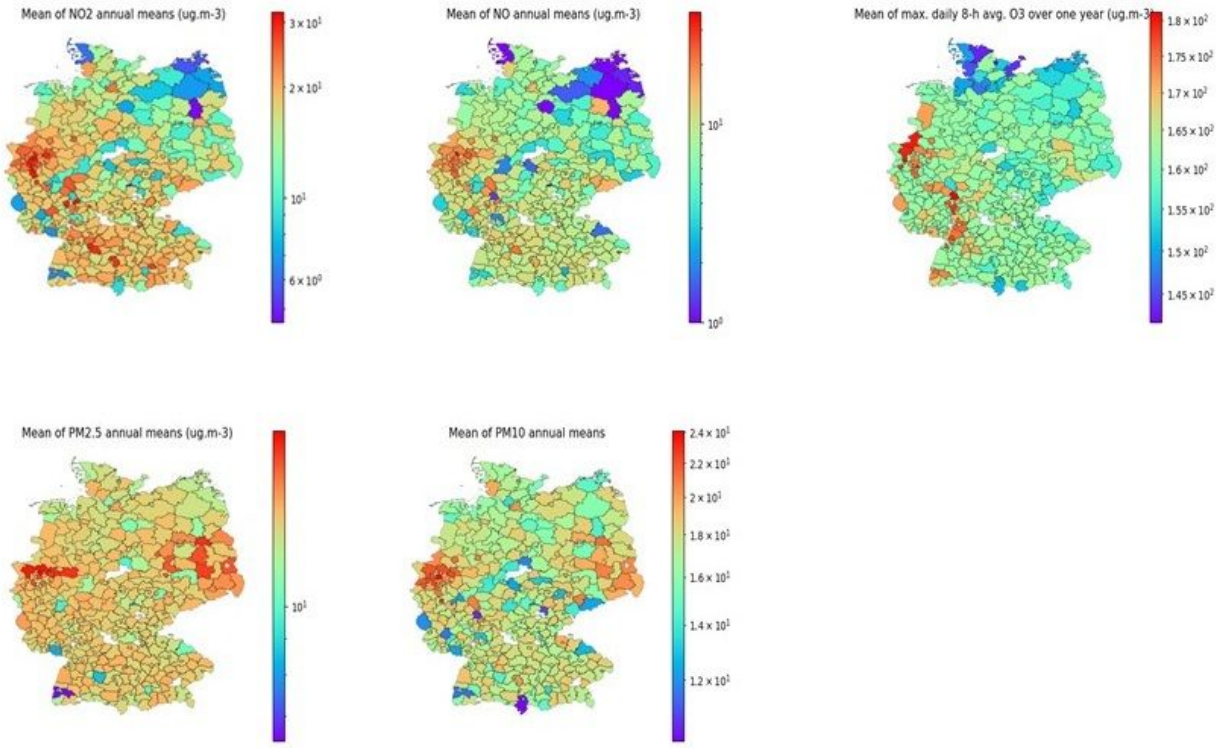

Figure 1

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.

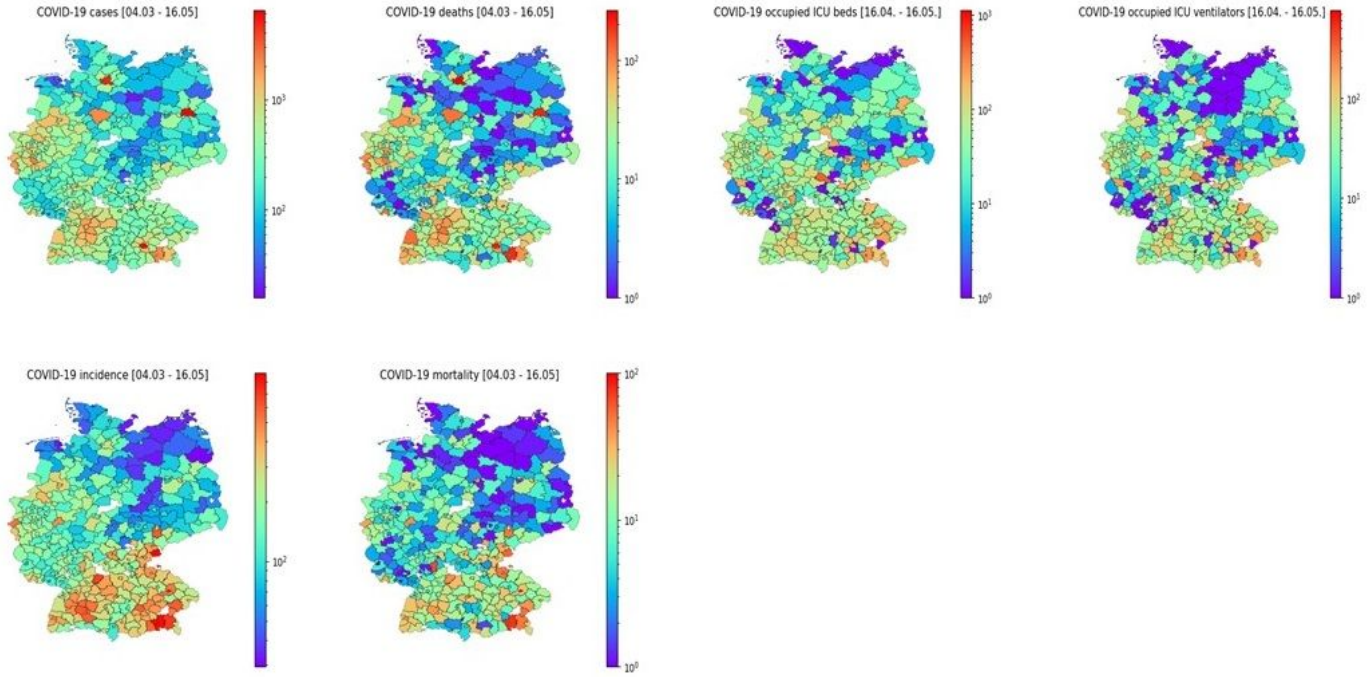

Figure 2

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.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementmaterialfinal.docx
- Table1.docx