Journal of Environmental Protection, 2022, 13, 508-526
https://www.scirp.org/journal/jep
ISSN Online: 2152-2219
ISSN Print: 2152-2197

Individual and Environmental Risk Factors for COVID-19 Mortality in Elderly in 7 European University Hospitals

Thomas Bourdrel[1*], Leo Zabrocki[2*], Nathalie Compte[3], Bert Bravenboer[3], Romain Decours[4], Hélène Pelerin[5], Laure De Decker[6], Laurence Le Jumeau de Kergaradec[7], Matthieu Lilamand[8], Claire Roubaud Baudron[9], Bertrand Fougère[10], Rachid Mahmoudi[11], Benoit Schorr[12], Georges Kaltenbach[12], Thomas Vogel[12], Vincent-Henri Puech[13], Fréderic Blanc[1], Marie-Abèle Bind[14]

[1]ICube Laboratory, UMR 7357 and CNRS, University of Strasbourg, Strasbourg, France
[2]Paris School of Economics, EHESS, Paris, France
[3]Geriatric Department, Universitair Ziekenhuis Brussel, Bruxelles, Belgium
[4]Service de Gériatrie, Centre hospitalier départemental de Vendée, La Roche Sur Yon, France
[5]Unité de recherche clinique, Centre hospitalier départemental de Vendée, La Roche Sur Yon, France
[6]Service de Médecine aigüe gériatrique Centre hospitalier universitaires de Nantes, Nantes, France
[7]Service de Gérontologie, Centre hospitalier universitaires de Nantes, Nantes, France
[8]Service de Gériatrie Assistance publique Hôpitaux de Paris (APHP) Nord, Paris, France
[9]Unité Post Urgences Gériatriques Centre hospitalier universitaire de Bordeaux, Hôpital Pellegrin, Bordeaux, France
[10]Department of Geriatric Medicine, Centre hospitalier universitaire de Tours, Tours, France
[11]Médecine Interne Gériatrie et Biologie du Vieillissement, Centre hopitalier universitaire de Reims, Reims, France
[12]Pôle de Gériatrie, La Robertsau Geriatric Hospital, University Hospital of Strasbourg, Strasbourg, France
[13]European Centre for Medium-Range Weather Forecasts, Copernicus Atmosphere Monitoring Service, London, UK
[14]Biostatistics Center, Massachusetts General Hospital, Boston, MA, USA

Email: thomasbourdrel@yahoo.fr, frederic.blanc@chru-strasbourg.fr, leo.zabrocki@gmail.com, nathalie.compte@uzbrussel.be, bert.bravenboer@uzbrussel.be, romain.decours@ght85.fr, helene.pelerin@ght85.fr, laure.dedecker@chu-nantes.fr, laurence.dekergaradec@chu-nantes.fr, matthieu.lilamand@aphp.fr, claire.roubaud@chu-bordeaux.fr, b.fougere@gmail.com, rmahmoudi@chu-reims.fr, georges.kaltenbach@chru-strasbourg.fr, benoit.schorr@chru-strasbourg.fr, thomas.vogel@chru-strasbourg.fr, Vincent-henri.peuch@ecmwf.int, ma.bind@mail.harvard.edu

How to cite this paper: Bourdrel, T., Zabrocki, L., Compte, N., Bravenboer, B., Decours, R., Pelerin, H., De Decker, L., Le Jumeau de Kergaradec, L., Lilamand, M., Baudron, C.R., Fougère, B., Mahmoudi, R., Schorr, B., Kaltenbach, G., Vogel, T., Puech, V.-H., Blanc, F. and Bind, M.-A. (2022) Individual and Environmental Risk Factors for COVID-19 Mortality in Elderly in 7 European University Hospitals. *Journal of Environmental Protection*, **13**, 508-526.
https://doi.org/10.4236/jep.2022.137032

Abstract

Because the elderly account for 80% of deaths from COVID-19 and they may be more vulnerable to air pollution, in this retrospective study we aimed to explore individual and environmental risk factors for COVID-19 mortality in the geriatric departments of seven European University hospitals, between February and May 2020. Long-term exposure to air pollution was estimated through annual pollutant concentrations at the residential address over the last two years. Short-term variations in air pollutants and weather parameters

*T. Bourdrel and L. Zabrocki contributed equally to this work.

Received: June 1, 2022
Accepted: July 16, 2022
Published: July 19, 2022

were also examined through a 20-day period before the confirmed PCR diagnostic of COVID-19. We found positive associations for diabetes and COVID-19 mortality (OR 2.2 CI 95%: 1.1, 4.4). Regarding environmental factors, we found no association between COVID-19 mortality and air pollutants and weather parameters; however, our study suffers from strong disparities—such as patient characteristics—between fairly polluted and less polluted cities. In order to overcome those disparities between cities, we aimed to explore the relationship between air pollution and COVID-19 mortality within each city, but even with the high-efficiency modelisation systems, differences in air pollutants were too small to estimate the effect of air pollution at the city level. Thus, this study highlights the need to improve the estimation of individual exposure to air pollution. To address this issue, solutions exist such as the increase of the number of fixed air monitors, or even better, through the use of individual markers of air pollution exposure such as urinary black carbon or passive individual samplers. Furthermore, we underline that outdoor air pollutant concentrations may not be representative of individual exposure, especially in the elderly, thus, we suggest that further studies focus on indoor air pollution. Regarding meteorological conditions, we found no association between UV, temperature, wind speed and COVID-19 mortality. We found a positive association between an increase in relative humidity (RH) and COVID-19 mortality, however, the influence of RH on COVID-19 mortality remains unclear, and additional studies are needed to confirm this potential link.

Keywords

COVID-19 Mortality, Air Pollution, Particulate Matter, Ultraviolet Radiation, Temperature

1. Introduction

Since November 2019, the world is facing a pneumonia epidemic due to a new coronavirus, severe acute respiratory syndrome (SARS)-associated coronavirus 2 (SARS-CoV-2), which leads to a disease named coronavirus disease 2019 (COVID-19) [1]. COVID-19 infections range from completely asymptomatic to severe forms requiring mechanical ventilation. When symptomatic, COVID-19 leads among other symptoms to lower respiratory tract infection, neurological impairment, cutaneous manifestations, or gastro-intestinal issues. Multiple organ failure, myopericarditis, pulmonary embolism, and acute respiratory distress syndrome represent the most serious complications of severe COVID-19. The elderly account for about 80% of deaths from COVID-19 [2]. COVID-19 comorbidities are still debated and may include hypertension, obesity, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and malignancy [3] [4] [5] [6]. As suggested for other respiratory viruses (e.g., SARS-CoV-1, influenza, respiratory syncytial virus, measles), several

studies are supporting the role of environmental exposures in COVID-19-related morbidity and mortality [6]. In particular, long-term exposure to air pollution through its impact on the development of cardiovascular and respiratory diseases or diabetes may be an aggravating factor for COVID-19 morbidity [6]. Short-term variations in air pollution and weather parameters such as temperature, relative humidity, boundary layer have been correlated with COVID-19 mortality, as well as with the spread of COVID-19 diseases [7] [8] [9] [10] [11]. While the elderly may be more vulnerable to adverse health effects of air pollution, studies exploring the influence of air pollution on COVID-19 mortality in this age group are missing. Indeed, most of the studies that explored individual and environmental risk factors for COVID-19 are US or Chinese surveys and the study population consisted of the overall population.

In this retrospective study, we investigated elderly patients who were hospitalized for COVID-19 in geriatric units in seven European hospitals, six in France and one in Belgium, see **Figure 1** Location of cities. These European cities are interesting to study, because they have different profiles in terms of air pollution and weather parameters. The study period was from February to May 2020, a period during which there was no vaccine or therapy for COVID-19.

Our main goal was to explore the influence of long-term exposure to outdoor air pollution on COVID-19 mortality.

Outdoor air pollution includes gaseous and particulate constituents. Of interest for COVID-19, particulate matter (PM) can be simplified into three classifications according to the size of particles, *i.e.*, coarse particles (PM10: diameter less than 10 μm), fine particles (PM2.5: diameter less than 2.5 μm), and ultrafine

Figure 1. Location of cities.

particles (PM0.1: diameter less than 0.1 μm). Depending on their source, PM can have different compositions. Carbonaceous PM from coal, fuel, or wood combustion have been suggested to be the most harmful and responsible for many chronic diseases, mainly cardiopulmonary diseases and cancer [12] [13]. The main outdoor gaseous pollutants include nitrogen dioxide (NO_2), ozone (O_3) and sulfur dioxide (SO_2). NO_2 is a major air pollutant in urban European cities, mainly arising from traffic, in particular from diesel cars [6]. O_3 is a secondary gaseous pollutant arising from atmospheric photochemical reactions involving sunlight (ultraviolet radiations) and gaseous precursors such as nitrogen oxide (NOx) or volatile organic compounds. As ozone formation requires atmospheric photooxidation of precursors (such as NO_2), its concentration also depends on meteorological conditions, such as heat and UV. Both O_3 and NO_2 have been associated with asthma and cardiovascular diseases [14].

We also explored if short-term variations in air pollutants and weather parameters had an impact on COVID-19 mortality. The main suspected COVID-19 comorbidities such as diabetes and hypertension (HTA) were also investigated.

2. Methods

2.1. Study Population

All patients were hospitalized for SARS-CoV-2 infection in geriatric units of university hospitals of six medium- to large-sized French cities, Strasbourg, Reims, Tours, Nantes, Paris, La Roche sur Yon, and the Belgium capital city, Bruxelles, between February and May 2020.

Admission criteria to admit a patient in geriatric unit was a minimum of 65 years of age.

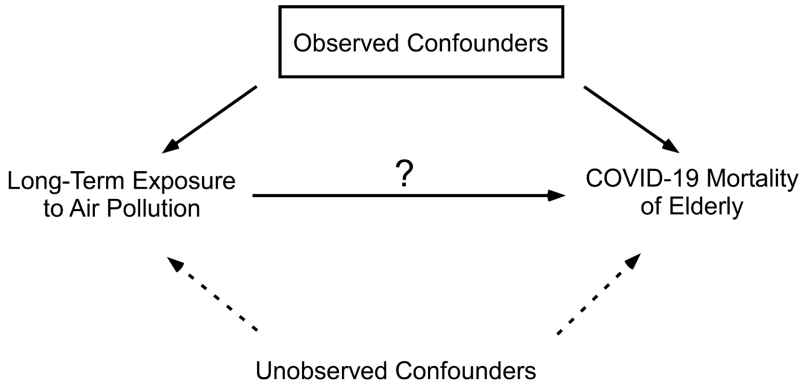
SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR). Because thoracic computerized tomography (CT) scanners were not available for all patients, we did not include thoracic CT examinations for the diagnosis of COVID-19. For all patients, we retrieved their residential address, sex, age, the date and positivy of their PCR test, and wether they died from COVID-19. According to literature data available at this period, the main suspected COVID-19 comorbidities: smoking status, body mass index (BMI), ischemic heart diseases, diabetes, hypertension, chronic renal failure, cancer, chronic obstructive pulmonary disease (COPD) were extracted from the medical records. Our main goal was to explore the link between long-term exposure to air pollution and COVID-19 mortality taking into account individual comorbidities.

The design of this retrospective study is shown in **Graph 1**.

In a second step, we also investigated the relationship between short-term variations in air pollution and weather parameters and COVID-19 mortality.

2.2. Environmental Exposures

Concerning air pollution, we focused on the main outdoor air pollutants (PM10, PM2.5, NO_2, O_3, and SO_2) whose concentrations were estimated at the residential address. Residential address was translated into Global Positioning System



Graph 1. Graphical abstract: Observed confounders are represented by patient characteristics (age, sex) and comorbidities.

(GPS) coordinates, encoded and transmitted anonymously to the European Centre for Medium Range Weather Forecasts (ECMWF), in charge of the European Commission's Copernicus program implementation (Modelling and Prediction|ECMWF). To ensure anonymity, we used only the name of the street and postcode, but not the street number. We obtained written informed consent to participate in the study from the patient's legal guardian. This study was approved by the Ethics Review Committee of the University Hospital of Strasbourg and all methods were carried out in accordance with relevant guidelines and regulations. We exclude patients with missing residential addresses and patients who moved during the last two years of the study period. We used annual pollutant concentrations averaged over the last two years of the study period as a proxy for long-term exposure to air pollution, and air pollutant concentrations averaged over the 20 day-period before the confirmed PCR diagnostic of COVID-19 as a proxy for short-term exposure to air pollution. According to previous studies. [6]-[11] we also obtained weather variables such as temperature, relative humidity (RH), ultraviolet radiation (UV), wind speed, and modelled pollen concentrations for birch, olive tree, grasses, and ragweed, over the 20 day-period before the confirmed PCR diagnostic of COVID-19 from the Copernicus program. Units of measure of environmental factors are detailed in **Supplementary Materials** Table SM1: Unit of measure of environmental exposure.

2.3. Statistical Analyses

We started with a descriptive analysis of patient characteristics (age, sex), patient comorbidities and COVID-19 mortality in the 7 cities.

Then, we investigated with a multivariate logistic regression model the association between COVID-19 mortality and patient characteristics and comorbidities: sex, age, BMI, active smoking, diabetes, hypertension, COPD, cardiac ischemic disease, renal failure, and cancer. We adjusted for the patient city.

Concerning long-term exposure to air pollution, we estimated the association between long-term exposure to an air pollutant and COVID-19 mortality using a multivariate logistic regression model. We fitted a separate model for each air

pollutant. We adjusted for patient characteristics (sex, age, BMI) and comorbidities (diabetes, hypertension, COPD, cardiac ischemic disease, renal failure, and cancer). We also adjusted for the patient city.

We investigated the short-term influence of air pollutants and weather parameters on COVID-19 mortality with a multivariate logistic regression model. We averaged daily exposure of environmental exposures over the 20 previous days before patients undertook a PCR test. We fitted a model for each environmental exposure in which we adjusted for sex, age, BMI, diabetes, hypertension, COPD, cardiac ischemic disease, renal failure, and cancer. We also took into account the patient city and the month of their PCR test.

Reproducibility:

All analyses were carried out with the R programming language (version 4.1.0). Although we were not allowed to share the data due to statistical confidentiality, we took great care to provide in the supplementary materials R Markdown documents where coding procedures are fully annotated.
https://github.com/lzabrocki/covid_air_pollution

3. Results

- We obtained data on 501 patients from seven cities (**Supplementary Materials** Table SM2: Number of Patients by City). The mean age was 83 years (standard deviation = 7.5). Female patients represent 49% of the patients. Several variables, such as active smoking and BMI, presented a non-negligible proportion of missing observations (**Supplementary Materials** Table SM3: Proportion of Missing Values by Patients' Characteristics).
- The proportion of COVID-19 deaths varied between cities ranging from more than 35% in Strasbourg to less than 20% in Tours and Reims, see Figure 2: COVID-19 mortality.

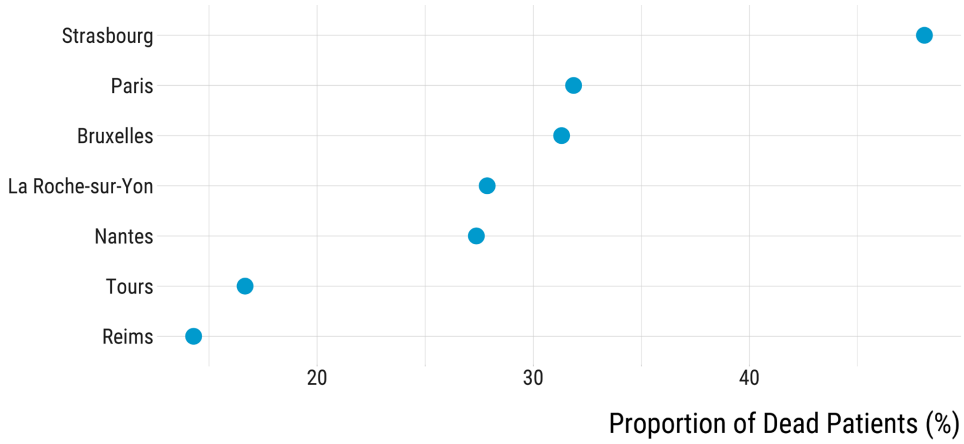


Figure 2. COVID-19 mortality.

- Patient characteristics were also different between cities in particular with regard to renal failure, COPD, ischemic cardiopathy, cancer, and diabetes, see Figure 3: Patient Characteristics by City.

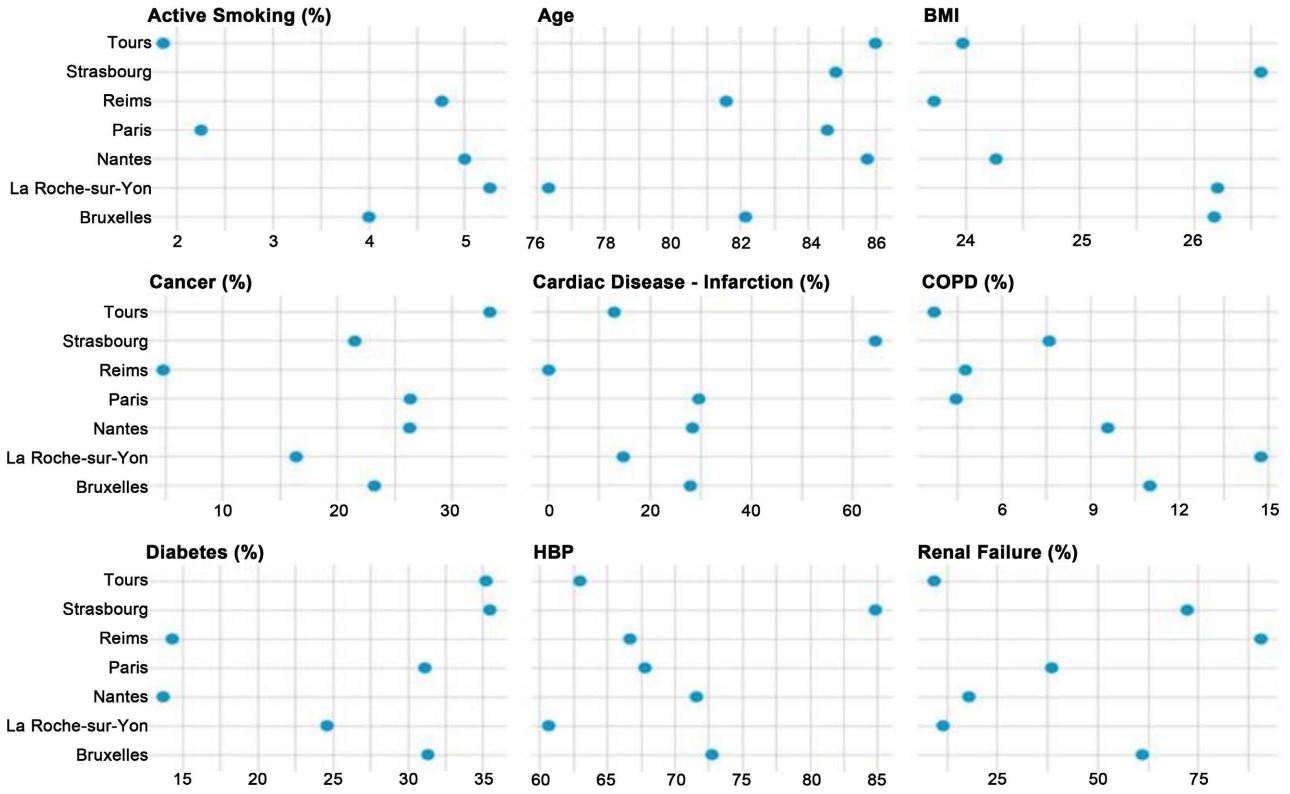


Figure 3. Patient characteristics by city.

- Comorbidities with the Odds of Dying from COVID-19:

Results from the analysis of co-morbidities and COVID-19 mortality are summarized in Table 1 (Table 1: Comorbidities with the Odds of Dying from COVID-19). We found only associations for diabetes (OR 2.2, CI 95%: 1.1, 4.4).

Table 1. Comorbidities with the odds of dying from COVID-19.

Variable	Point Estimate	95% CI
Sex (male)	1.1	(0.6, 2.2)
Age	1	(1.0, 1.1)
BMI	1	(0.9, 1.0)
Active Smoking	0.5	(0.0, 3.3)
Diabetes	2.2	(1.1, 4.4)
HBP	1.4	(0.7, 2.9)
COPD	0.5	(0.1, 1.4)
Cardiac Ischemic Disease	1.1	(0.5, 2.4)
Renal Failure	1.2	(0.6, 2.6)
Cancer	1.6	(0.8, 3.4)

- Figure 4 illustrates the average in air pollutant concentrations between 2017 and 2019 by city (Figure 4: Average Air Pollutant Concentrations (2017-2019) by City). PM10 levels ranged from 19.6 to 11.3 μg/m^3, PM2.5 from 13.5

to 7 µg/m^3 and NO_2 from 27.3 to 3.2 µg/m^3. Ozone concentrations ranged from 60 to 43.9 µg/m^3. We observed differences in air pollution exposure between cities: Paris and Bruxelles had the highest levels of PM10, PM2.5 and NO_2 followed by Strasbourg and Reims, while Nantes, Tours and La Roche-sur-Yon had the lowest levels. We also investigated whether air pollution exposures were linked to co-morbidities, and we observed some correlations between PM10 and cancer (OR: 1.5, CI 95%: 1.1, 2.1) and between PM2.5 and cancer (OR: 1.5, CI 95%: 1.1, 2.3), see Figure 5: Long-Term Exposure to Air Pollution and Comorbidities.

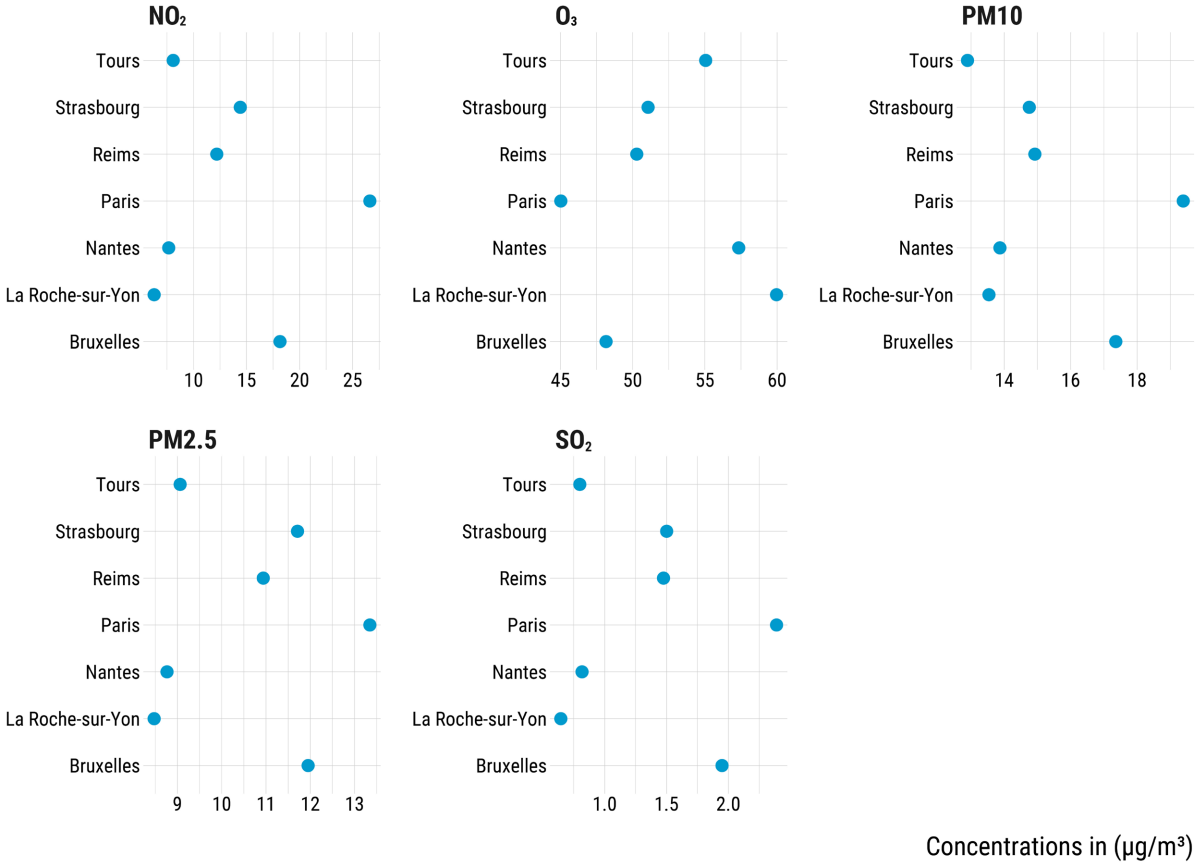


Figure 4. Average air pollutant concentrations (2017-2019) by city.

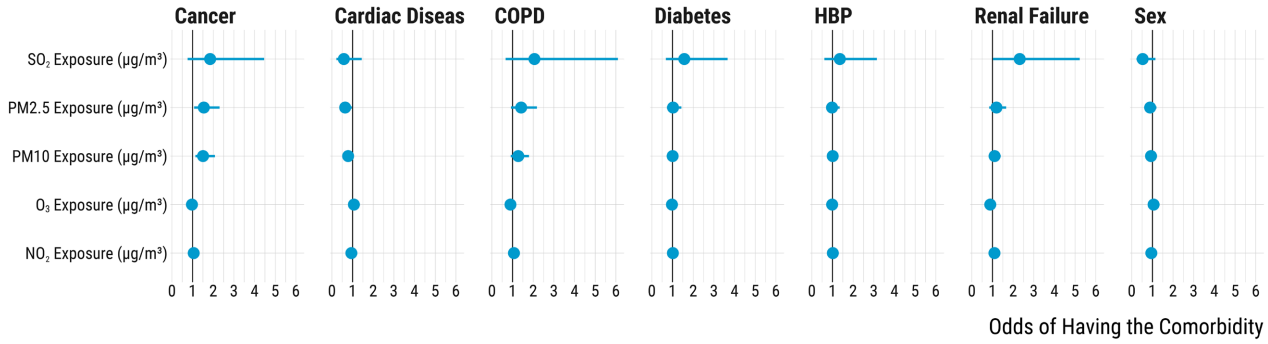


Figure 5. Long-term exposure to air pollution and comorbidities.

- Long-term exposure to air pollution and COVID-19 mortality (Figure 6 and Table 2):

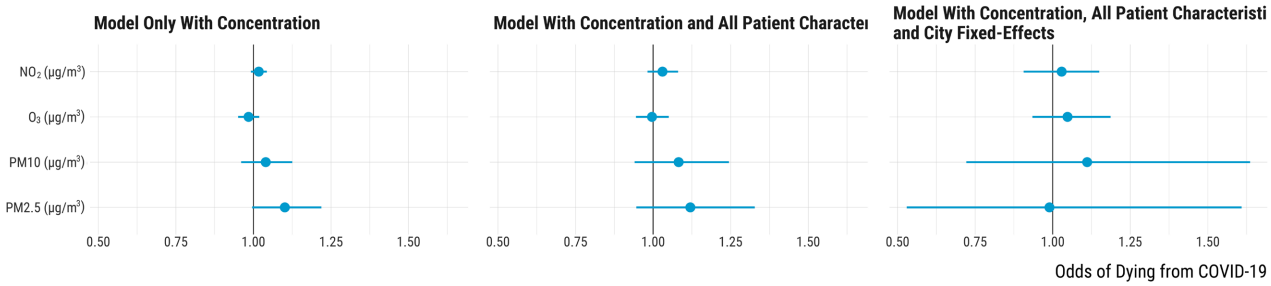


Figure 6. Long-term air pollution and COVID-19 mortality.

Table 2. Long-term exposure to air pollution and COVID-19 mortality.

Air Pollutant	Model	Point Estimate	95% CI
NO_2	Model With Concentration and All Patient Characteristics	1.03	(0.98, 1.08)
NO_2	Model With Concentration, All Patient Characteristics and City Fixed-Effects	1.03	(0.92, 1.15)
O_3	Model With Concentration and All Patient Characteristics	1	(0.95, 1.05)
O_3	Model With Concentration, All Patient Characteristics and City Fixed-Effects	1.05	(0.93, 1.18)
PM10	Model With Concentration and All Patient Characteristics	1.08	(0.94, 1.24)
PM10	Model With Concentration, All Patient Characteristics and City Fixed-Effects	1.11	(0.75, 1.63)
PM2.5	Model With Concentration and All Patient Characteristics	1.12	(0.95, 1.33)
PM2.5	Model With Concentration, All Patient Characteristics and City Fixed-Effects	0.99	(0.59, 1.67)

After adjustment for all patient characteristics and city, our data did not allow us to report an association between long-term exposure to NO_2, O_3 and PM10 and the odds of dying from COVID-19. Concerning PM2.5, in the non-adjusted model, we found that a 1 µg/m^3 increase in long-term exposure to PM2.5 was associated with a positive increase in the odds of dying from COVID-19. However, when adjusted for patient characteristics and city, we found no association; see Figure 6 and Table 2: Long-term exposure to air pollution and COVID-19 mortality.

In order to overcome the disparities in patient characteristics between fairly polluted and less polluted cities, we tried to analyze the link between air pollution and COVID-19 mortality within each city. Unfortunately, even with the high efficiency modelisation systems used by the Copernicus program, differences in air pollutant concentrations within each city were too small and did not allow such analysis.

- Short-Term Environmental Exposure and COVID-19 mortality (Figure 7 and Table 3):

Regarding the influence of short term exposure to air pollutants, pollens on COVID-19 mortality, we found no association. However, the study of pollens is limited by the fact that our study period mainly concerns winter months during which no significant pollen concentrations were measured.

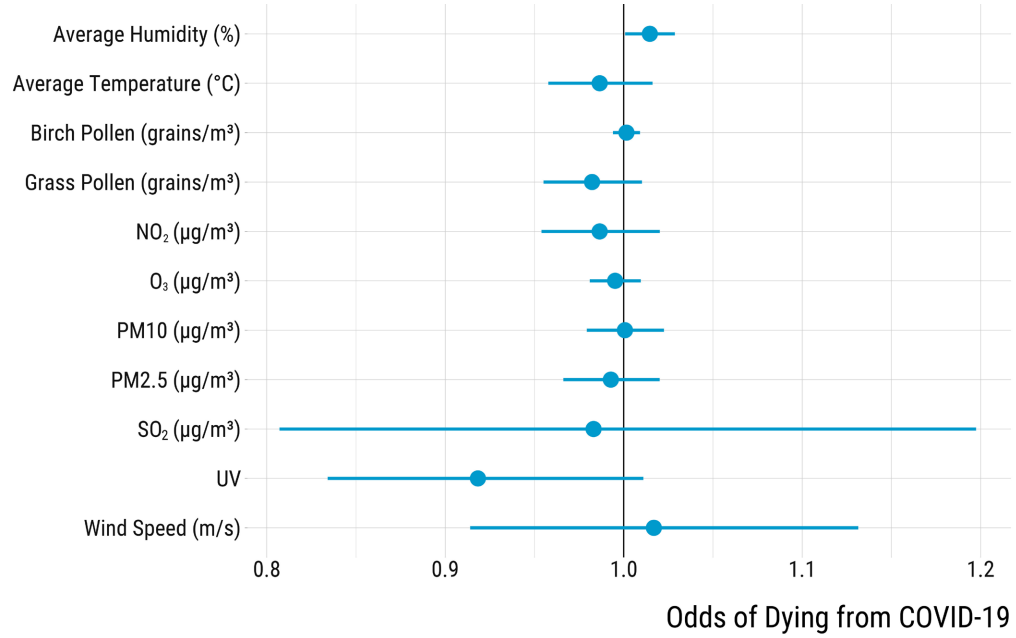


Figure 7. Short-term exposure COVID-19 mortality.

Table 3. Short-term environmental exposure and COVID-19 mortality.

Exposure	Point Estimate	95% CI
Average Humidity (%)	1.01	(1.0, 1.03)
Average Temperature (˚C)	0.99	(0.96, 1.02)
Birch Pollen (grains/m^3)	1	(0.99,1.01)
Grass Pollen (grains/m^3)	0.98	(0.96, 1.01)
NO_2 (µg/m^3)	0.99	(0.95, 1.02)
O_3 (µg/m^3)	1	(0.98, 1.01)
PM10 (µg/m^3)	1	(0.98, 1.02)
PM2.5 (µg/m^3)	0.99	(0.97,1.02)
SO_2 (µg/m^3)	0.98	(0.81, 1.2)
UV	0.92	(0.83, 1.01)

Concerning weather parameters, the risk of dying from COVID-19 was increased by 1.01 (CI 95%: 1.00 - 1.03) for a 1% increase in average humidity. Regarding temperature, wind speed and UV index, our data did not allow us to report an association with the odds of dying from COVID-19 (0.99 CI 95%: 0.96 - 1.02 and 0.92 CI 95% 0.83 - 1.01, respectively). Figure 7 and Table 3: Short-Term Environmental Exposure and COVID-19 mortality.

4. Discussion

4.1. Individual Comorbidities and COVID-19 Mortality

Regarding individual risk factors, our results indicated that diabetes was asso-

ciated with a two-fold increased in the odds of dying from COVID-19, which is in line with the results published by previous studies on the main risk factors of COVID-19 mortality [2] [15]. We found no association between COVID-19 mortality and BMI, sex, hypertension, renal failure, and cancer.

Our study suffers from limitations in the exploration of individual comorbities, for instance we did not consider the socio-economic status or the occupation of selected people throughout their working life. In addition, other suspected comorbidities have not been explored such as immunodepression. As it will be discussed further below, to focus on COVID-19 outcomes only in terms of mortality without exploring biological parameters such as systemic inflammation, CT scan severity, or admission rate in resuscitation units is also a main limitation.

4.2. Exposure to Air Pollution on COVID-19 Mortality

Regarding the influence of air pollution on COVID-19 mortality, in the adjusted models with all patient characteristics, we found no association between both long-term and short-term increase in air pollutants and the odds of dying from COVID-19. Adjustment with the city indicator highlights disparities between highly and less polluted cities. Indeed, our study revealed differences in COVID-19 mortality between cities that were only partially explained by differences in comorbidities and environmental factors. Other differences between cities such as diet, socio-economic status, or differences in health management, may explain those differences. As an example, accessibility to reanimation and intensive care units may differ between cities, for instance, during this period, intensive care units in Strasbourg and Paris were close to saturation. Even if we do not have the proportion of patients admitted in intensive care units in each city, it is most likely that such differences may have played a role in patient survival. Moreover, our study concerns the first wave of the COVID-19 pandemic, a period during which little was known about COVID-19 management and treatment, which may have led to differences in patient outcomes. For example, some geriatric centers may have introduced corticotherapy and anticoagulants therapies - treatment that has been shown to be effective on survival - whereas others did not in the absence of available scientific evidence at this time of the epidemic.

In order to overcome disparities between cities, it would have been helpful to compare the influence of air pollution on COVID-19 mortality within each city, but, even with the high-efficiency modelisation systems used by European Centre for Medium Range Weather Forecasts, we were unable to provide estimates of the effect of air pollution at the city level, because differences in air pollution concentrations were too small. Thus, our study highlights the limits of modelisation systems. Indeed, within the same city, air pollution may strongly differ from one street to another, depending on proximity to road traffic or local sources of air pollution, but those differences are underestimated by modelisation systems. To address this issue, a solution would be to increase the number of fixed monitors measuring air quality; for example in Strasbourg there are only 5 fixed mon-

itors for the 400,000 inhabitants. Individual markers to air pollution exposure may also solve this issue. For example, urinary black carbon is accurately correlated with the exposure to air pollution from combustion sources, such as diesel cars, wood, and coal heating [16]. Previous studies reported that urinary levels of black carbon strongly differ from one street to another, as a function to the distance from to a main road [16]. Personal passive samplers will also be helpful to improve estimation of individual exposure to air pollutants [17]. Difficulties to correctly address air pollution exposure have been highlighted in previous studies. Indeed, regarding outdoor air pollution exposure, most previous studies exploring air pollution and COVID-19 mortality have used regional-level data that may lead to inaccuracies in air pollution exposure [18]. As a consequence, our study design with individual-level data based on residential address may be more reliable, but as we discussed before, even individual-level data are imprecise surrogates for personal air pollution exposure due to the limits of modelisation systems. As an example, Travaglio *et al.* used individual-level data from the UK Biobank and found contradictory results depending on the resolution of the modelisation system used for the estimation of air pollution at residential address [19]. Limitation of this study also concerns long-term exposure to air pollution that has been estimated through the residential address of the previous two years, which may have led to important misclassification, in particular if patients moved before those two years. In addition, air pollution exposure over the last two years may not be enough representative of long term exposure to air pollution which would require a longer period of exposition. Furthermore, outdoor air pollutant concentrations may not be representative of individual exposure as elderly patients spend most of their time inside, thus, we suggest that further studies focus on indoor air pollution.

Even though our study does not point to a conclusive link between COVID-19 mortality and air pollution, several studies reported associations between long-term exposure to air pollution and COVID-19 mortality. A Harvard study reported that 1 $\mu g/m^3$ increase in long-term exposure to PM2.5 was associated with an increase in COVID-19 mortality by 11% (95% CI, 6 to 17%) [20]. Munzel *et al.* concluded that 15% - 18% (95% confidence interval 7% - 33%) of COVID-19 related-deaths may be attributable to air pollution [21]. Several mechanisms may explain the impact of air pollution on COVID-19 mortality, e.g, it is agreed that long-term exposure to air pollution is associated with an increased risk of chronic diseases, such as ischemic cardiac diseases, lung cancer, COPD, lung fibrosis, diabetes, which are the main suspected co-factors of COVID-19 morbidity and mortality [6]. Furthermore, in-vitro, animals, and human studies demonstrated that even short-term increases in air pollutant exposures lead to a decrease in immune respiratory defense, such as macrophage phagocytosis and antimicrobial peptides [6]. Air pollution may also facilitate viral entry due to increased mucosal permeability and activation of protease, which drive the activation of the spike protein [6]. In addition, air pollution may increase renin-angiotensin-aldosterone system (RAAS) and Angiotensin II receptor type 1 activity,

and thus, may lead to a more severe form of the disease [6]. This brings us to another limitation of our study as we focused on COVID-19 outcomes only in terms of mortality; we recommend that biological parameters such as systemic inflammation, CT scan severity, admission rate in resuscitation units, should be explored in future studies in order to explore the link between air pollution and severity of COVID-19. Air pollution also has indirect harmful effects, for instance, related to lower proportion of UV radiations reaching the atmosphere, air pollution is also associated with reduced levels of vitamin D, which plays an important role in immune response [6].

Our study suffers from other limitations, such as missing data on patient's characteristics (e.g., socio-economic status, racial disparities). However, we do believe that, in European cities, such differences are less pronounced and less significant than in the US for instance [22]. Another limitation is that we did not examine the differences between nursing home residents and patients living at home. Nursing home residents may be more vulnerable than independent patients living at home.

4.3. Weather Parameters and COVID-19 Mortality

Regarding weather parameters, we found a positive association between an increase in relative humidity and COVID-19 mortality; however the influence of RH on COVID-19 mortality remains unclear, indeed previous studies reported both positive and negative associations between RH and COVID-19 mortality [23].

We found no association between UV index, wind speed, temperature and COVID-19 mortality. Previous studies reported that increase in UV index may lead to decrease COVID-19 mortality, which could be explained by the fact that atmospheric UV may have virucidal activity and are also necessary for vitamin D synthesis whose deficiency has been linked with sever forms of COVID-19 [6] [24]. Concerning temperature, previous results from a large study—which explored the OECD countries and the United States—reported that a 1˚C increase in ambient temperature was associated with a decrease by 6% of COVID-19 mortality in the next 30 days [11].

In addition to their potential role on COVID-19 mortality, weather variables may be also linked to the spread of the disease [25] [26]. In particular, temperature and wind speed have been negatively associated with the spread of COVID-19 [9]. Among other effects, low temperature may reduce the functioning of airways ciliated cells. In addition, weather conditions as temperature, UV and RH may influence the persistence of viral droplets [6]. Indeed, experimental studies found that SARS-CoV-2 was more stable at low humidity and lower temperatures [6] [11]. Relative humidity, wind speed and temperature may influence hydration and desiccation of viral droplets, and thus may influence the size and contagiousness of droplets [6]. Previous studies also supported that high wind speed may reduce SARS-CoV-2 transmission, as it is associated with a higher

ventilation coefficient [9].

5. Conclusion

In this study exploring environmental and individual risk factors for COVID-19 mortality in geriatric units from seven European University hospitals, we found that diabetes status was associated with a 2-fold increase in the odds of dying from COVID-19. Concerning air pollution exposure, while several studies found that air pollution may increase COVID-19 severity and mortality, we could not reject the null hypothesis of no association between both long-term and short-term exposure and COVID-19 mortality. However, our study suffers from disparities between highly and less polluted cities such as patient profiles or health management. In addition because of the inherent limits of modelisation systems of air pollution exposure, we were not able to estimate the effect of air pollution on COVID-19 mortality within each city. Thus, our study highlights the need for an improved modelisation system at the city level. In the future, individual markers such as urinary black carbon may be helpful to provide a better estimation of individual exposure to air pollution. Upcoming studies should also discuss indoor air pollution and COVID-19 severity, as everyone, especially the elderly, spends most of their time inside. Regarding meteorological conditions, while previous studies reported that an increase in UV, temperature and wind speed may be associated with a decrease in COVID-19 transmission and mortality, we found no association between UV, temperature and COVID-19 mortality.

Sources of Funding

Research reported in this publication was supported by the Office of the Director, National Institutes of Health under Award Number DP5OD021412. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Code Availability

https://github.com/lzabrocki/covid_air_pollution

Author Contributions

T.Bourdrel, F.Blanc and Marie-Abèle Bind contributed to the study conception and design. All autors contributed to data collection. Stastistical analysis were performed by Léo Zabrocki and Marie-Abèle Bind. The first draft of the manuscript was written by T.Bourdrel and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

This study was approved by the Ethics Review Committee of the University Hospital of Strasbourg (CE-2020-95/RNI 2020 HUS N˚ 7922). All methods were

carried out in accordance with relevant guidelines and regulations.

Consent to Participate

We obtained written informed consent to participate in the study from the patient's legal guardian.

Conflicts of Interest

The authors declare no competing interests.

References

[1] Zhu, N., Zhang, D., Wang, W., *et al.* (2020) China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England Journal of Medicine*, **382**, 727-733. https://doi.org/10.1056/NEJMoa2001017

[2] Blanc, F., Waechter, C., Vogel, T., *et al.* (2021) Therapeutic Prevention of COVID-19 in Elderly: A Case-Control Study. *GeroScience*, **43**, 2333-2343. https://doi.org/10.1007/s11357-021-00397-z

[3] Semenzato, L., Botton, J., Drouin, J., Cuenot, F., Dray-Spira, R., Weill, A. and Zureik, M. (2021) Chronic Diseases, Health Conditions and Risk of COVID-19-Related Hospitalization and In-Hospitalmortality during the First Wave of the Epidemic in France: A Cohort Study of 66 Million People. *The Lancet Regional Health-Europe*, **8**, Article ID: 100158. https://doi.org/10.1016/j.lanepe.2021.100158

[4] Cueto-Manzano, A.M., Espinel-Bermúdez, M.C., Hernández-González, S.O., *et al.* (2021) Risk Factors for Mortality of Adult Patients with COVID-19 Hospitalised in an Emerging Country: A Cohort Study. *BMJ Open*, **11**, e050321. https://doi.org/10.1136/bmjopen-2021-050321

[5] Guan, W.J., Liang, W.H., Zhao, Y., Liang, H.R., *et al.* (2020) China Medical Treatment Expert Group for COVID-19. Comorbidity and Its Impact on 1590 Patients with COVID-19 in China: A Nationwide Analysis. *European Respiratory Journal*, **55**, Article ID: 2000547. https://doi.org/10.1183/13993003.00547-2020

[6] Bourdrel, T., Annesi-Maesano, I., Alahmad, B., Maesano, C.N. and Bind, M.A. (2021) The Impact of Outdoor Air Pollution on COVID-19: A Review of Evidence from *in vitro*, Animal, and Human Studies. *European Respiratory Review*, **30**, Article ID: 200242. https://doi.org/10.1183/16000617.0242-2020

[7] Rohrer, M., Flahault, A. and Stoffel, M. (2020) Peaks of Fine Particulate Matter May Modulate the Spreading and Virulence of COVID-19. *Earth Systems and Environment*, **4**, 789-796. https://doi.org/10.1007/s41748-020-00184-4

[8] Dragone, R., Licciardi, G., Grasso, G., Del Gaudio, C. and Chanussot, J. (2021) Analysis of the Chemical and Physical Environmental Aspects that Promoted the Spread of SARS-CoV-2 in the Lombard Area. *International Journal of Environmental Research and Public Health*, **18**, Article No. 1226. https://doi.org/10.1007/s41748-020-00184-4

[9] Chelani, A.B. and Gautam, S. (2022) The Influence of Meteorological Variables and Lockdowns on COVID-19 Cases in Urban Agglomerations of Indian Cities. Stochastic Environmental Research and Risk Assessment. https://doi.org/10.1007/s00477-021-02160-4

[10] Wu, Y., Jing, W.z., Liu, J., Ma, Q.y., Yuan, J., Wang, Y.p., Du, M. and Liu, M. (2020) Effects of Temperature and Humidity on the Daily New Cases and New Deaths of COVID-19 in 166 Countries. *Science of the Total Environment*, **l729**, Article ID: 139051. https://doi.org/10.1016/j.scitotenv.2020.139051

[11] Christophi, C.A., Sotos-Prieto, M., Lan, F.Y., *et al.* (2021) Ambient Temperature and Subsequent COVID-19 Mortality in the OECD Countries and Individual United States. Scientific Reports, **11**, Article No. 8710. https://doi.org/10.1038/s41598-021-87803-w

[12] Bourdrel, T., Bind, M.A., Béjot, Y., Morel, O. and Argacha, J.F. (2017) Cardiovascular Effects of Air Pollution. *Archives of Cardiovascular Diseases*, **110**, 634-642. https://doi.org/10.1016/j.acvd.2017.05.003

[13] Schraufnagel, D.E., Balmes, J.R., Cowl, C.T., *et al.* (2019) Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 1: The Damaging Effects of Air Pollution. *Chest*, **155**, 409-416. https://doi.org/10.1016/j.chest.2018.10.042

[14] Atkinson, R.W., Butland, B.K., Anderson, H.R. and Maynard, R.L. (2018) Long-Term Concentrations of Nitrogen Dioxide and Mortality. *Epidemiology*, **29**, 460-472. https://doi.org/10.1097/EDE.0000000000000847

[15] Wu, Z., Tang, Y. and Cheng, Q. (2021) Diabetes Increases the Mortality of Patients with COVID-19: A Meta-Analysis. *Acta Diabetol*, **58**, 139-144. https://doi.org/10.1007/s00592-020-01546-0

[16] Saenen, N.D., Bové, H., Steuwe, C., Roeffaers, M.B.J., *et al.* (2017) Children's Urinary Environmental Carbon Load. A Novel Marker Reflecting Residential Ambient Air Pollution Exposure? *American Journal of Respiratory and Critical Care Medicine*, **196**, 873-881. https://doi.org/10.1164/rccm.201704-0797OC

[17] Mendoza-Sanchez, I., Uwak, I., Myatt, L., *et al.* (2021) Maternal Exposure to Polycyclic Aromatic Hydrocarbons in South Texas, Evaluation of Silicone Wristbands as Personal Passive Samplers. *Journal of Exposure Science and Environmental Epidemiology*, **32**, 280-288. https://doi.org/10.1038/s41370-021-00348-y

[18] Berg, K., Romer Present, P. and Richardson, K. (2021) Long-Term Air Pollution and Other Risk Factors Associated with COVID-19 at the Census Tract Level in Colorado. *Environmental Pollution*, **287**, Article ID: 117584. https://doi.org/10.1016/j.envpol.2021.117584

[19] Travaglio, M., Yu, Y., Popovic, R., Selley, L., Leal, N.S. and Martins, L.M. (2021) Links between Air Pollution and COVID-19 in England. *Environmental Pollution*, **268**, Article ID: 115859. https://doi.org/10.1016/j.envpol.2020.115859

[20] Wu, X., Nethery, R.C., Sabath, M.B., Braun, D. and Dominici, F. (2020) Air Pollution and COVID-19 Mortality in the United States: Strengths and Limitations of an Ecological Regression Analysis. *Science Advances*, **6**, eabd4049. https://doi.org/10.1126/sciadv.abd4049

[21] Andrea, P., Francesca, D., Andy, H., Christian, W., Thomas, M. and Jos, L. (2020) Regional and Global Contributions of Air Pollution to Risk of Death from COVID-19. Cardiovascular Research, **116**, 2247-2253. https://doi.org/10.1093/cvr/cvaa288

[22] Brandt, E.B., Beck, A.F. and Mersha, T.B. (2020) Air pollution, racial disparities, and COVID-19 mortality. *The Journal of Allergy and Clinical Immunology*, **146**, 61-63. https://doi.org/10.1016/j.jaci.2020.04.035

[23] Romero Starke, K., Mauer, R., Karskens, E., Pretzsch, A., Reissig, D., Nienhaus, A., Seidler, A.L. and Seidler, A. (2021) The Effect of Ambient Environmental Condi-

tions on COVID-19 Mortality: A Systematic Review. *International Journal of Environmental Research and Public Health*, **18**, Article 6665. https://doi.org/10.3390/ijerph18126665

[24] Gorman, S. and Weller, R.B. (2020) Investigating the Potential for Ultraviolet Light to Modulate Morbidity and Mortality from COVID-19: A Narrative Review and Update. *Frontiers in Cardiovascular Medicine*, **7**, Article 616527. https://doi.org/10.3389/fcvm.2020.616527

[25] Mejdoubi, M., Djennaoui, M. and Kyndt, X. (2021) Link between COVID-19-Related in-Hospital Mortality in Continental France Administrative Areas and Weather: An Ecological Study. *BMJ Open*, **11**, e043269. https://doi.org/10.1136/bmjopen-2020-043269

[26] Solimini, A., Filipponi, F., Fegatelli, D.A., *et al.* (2021) A Global Association between Covid-19 Cases and Airborne Particulate Matter at Regional Level. *Scientific Reports*, **11**, Article No. 6256. https://doi.org/10.1038/s41598-021-85751-z

Abbreviations

PM: particulate matter;
NO_2: nitrogen dioxide;
O_3: ozone;
SO_2: sulfur dioxide;
HBP: high blood pressure (hypertension);
COVID-19: coronavirus disease 2019;
SARS-CoV-2: severe acute respiratory syndrome (SARS)-associated coronavirus 2;
COPD: chronic obstructive pulmonary disease;
BMI: body mass index;
RT-PCR: reverse transcriptase polymerase chain reaction
UV: ultraviolet radiation;
RH: relative humidity;
T°: temperature;
OR: odd ratio;
CI: confidence interval;
RAAS: renin-angiotensin-aldosterone system.

Supplementary Materials Table

Table SM1. Unit of measure of environmental exposure.

Environmental Exposure	Unit
10-metre wind speed	m/s
birch pollen count	grains/m^3
boundary layer height	m
grass pollen count	grains/m^3
nitrogen dioxide	µg/m^3
ozone	µg/m^3
olive pollen count	grains/m^3
particulate matter < 10 um	µg/m^3
particulate matter < 2.5 um	µg/m^3
relative humidity	%
sulphur dioxide	µg/m^3
2-metre temperature	°C
UV index	dimensionless index

Table SM2. Number of patients by city.

City	Number of Patients
Bruxelles	100
La Roche-sur-Yon	61
Nantes	95
Paris	91
Reims	21
Strasbourg	79
Tours	54

Table SM3. Proportion of missing values by patients' characteristics.

Variable	Missing (%)
BMI	28.1
Active Smoking	27.9
COPD	0.4
Diabetes	0.4
HBP	0.4
Cancer	0.2
Dead	0.2
Age	0
Cardiac Disease Infarction	0
COVID	0
Renal Failure	0