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NO₂ levels as a contributing factor to COVID-19 deaths: The first empirical estimate of threshold values

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ABSTRACT

This study represents the first empirical estimation of threshold values between nitrogen dioxide (NO₂) concentrations and COVID-19-related deaths in France. The concentration of NO₂ linked to COVID-19-related deaths in three major French cities were determined using Artificial Neural Networks experiments and a Causal Direction from Dependency (D2C) algorithm. The aim of the study was to evaluate the potential effects of NO₂ in spreading the epidemic. The underlying hypothesis is that NO₂, as a precursor to secondary particulate matter formation, can foster COVID-19 and make the respiratory system more susceptible to this infection. Three different neural networks for the cities of Paris, Lyon and Marseille were built in this work, followed by the application of an innovative tool of cutting the signal from the inputs to the selected target. The results show that the threshold levels of NO₂ connected to COVID-19 range between 15.8 µg/m³ for Lyon, 21.8 µg/m³ for Marseille and 22.9 µg/m³ for Paris, which were significantly lower than the average annual concentration limit of 40 µg/m³ imposed by Directive 2008/50/EC of the European Parliament.

1. Introduction

The Corona Virus Disease (COVID-19) was qualified as a global health emergency on March 12th 2020 by the World Health Organization (WHO) (WHO, 2020a). At the world level and as of August 16th 2020, WHO reported 761,779 confirmed deaths and 21,294,845 confirmed cases. The virus is known to spread through three known channels: saliva, nasal discharge, or airborne particles (Mitra et al., 2020). The symptoms are generally pneumonia, fever and dyspnoea. Even though it is admitted that most infected patients recover without advanced treatment, elderly and sensitive people present an important risk to develop severe and fatal complications with a fatality rate of approximately 2–3% (Mitra et al., 2020; Rodriguez-Morales et al., 2020). Washing hands with alcohol-based hand sanitizer is unanimously seen as one of the effective ways to prevent and reduce transmission worldwide. In addition, experts seem unanimous on the necessity to reduce contact among the population. This would not only protect unaffected individuals, but also isolate the carriers of the virus. Therefore, the quarantine strategy has been adopted by most governments to

control the virus propagation (Mitra et al., 2020).

As the epicentre of the pandemic, China first decided to impose a strict containment system on its population (Huang et al., 2020). Following that, identical health measures were adopted by numerous governments, notably in France. Beginning from March 17th 2020, the French President Emmanuel Macron decreed the state of sanitary emergency and implemented a national containment measure (i.e., closing down schools, colleges and universities; shutting down commercial activities and sending employees home, restricting public transport services; prohibiting rallies and meetings in public spaces; obligation for individuals to stay in their residence). However, serious consequences are unfortunately expected with respect to the economy. While most of the industries (notably aeronautic and automotive) are running idle in France, other essential sectors (i.e., agriculture, tourism, culture) are undergoing through a major restructure to find back the lost path of prosperity.

Economic activity is known to be a leading contributor to global environmental pollution. Greenhouse gas (GHG) emissions are directly released into the atmosphere through fuel combustion

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(Intergovernmental Panel on Climate Change, IPCC, 2007). In major world cities, air is considered polluted when high concentrations of harmful particles are recorded (Anjum, 2020). Among them, one generally finds primary pollutants (methane, CH₄; carbon monoxide, CO; nitrogen oxide, NO_x; nitrogen dioxide, NO₂; sulphur dioxide, SO₂) but also secondary pollutants (ozone, O₃; sulphur trioxide, SO₃). Furthermore, measuring critical concentrations of particulate matter (PM₁₀ and PM_{2.5}) in urban areas is now unsurprising. Mainly emitted by transport, power stations, heating plants, off-road equipment and industrial processes (Jol and Kielland, 1997; Goudarzi et al., 2012), the concentration of nitrogen dioxide (NO₂) is drawing the attention from researchers in Europe. The summation of NO₂ (nitrogen dioxide) and NO (nitric oxide) is called NO_x (nitrogen oxide). In turn, NO_x contributes to formation of secondary particles through transformation via photochemical reactions of nitric acid (HNO₃) and ozone (O₃) (Khoder, 2002; Nguyen et al., 2015). Notably, these particles can directly contribute to the acidity of rainwater (Waller et al., 2012). Mega-cities in the developing world are dealing with closely related challenges, directly linked with the increased proportion of diesel cars in the automobile fleet (Mavroidis and Chaloulakou, 2011).

Exposure to air pollution induces adverse health effects for the population,¹ including respiratory, infections, asthma, allergic rhinitis and eczema in children, chronic obstructive pulmonary and heart disease, and lung cancer (Pant and Harrison, 2013; Kim et al., 2018; Chen et al., 2019; To et al., 2020). It has been shown that short and long term exposures to NO₂ concentrations may produce hypertension and diabetes, lung damage, heart and cardiovascular diseases, and significant respiratory mortality (Nakai et al., 1995; Department of the Environment of Great Britain, 1996; Hoek et al., 2002; Beelen et al., 2008; Gan et al., 2012; Goudarzi et al., 2012; Saeha et al., 2020). Blomberg et al. (1999) demonstrated that the immune system's reaction to NO₂ exposure is directly observable through important airway inflammation. Overall, it has been shown that high NO₂ concentration levels are expected to produce more adverse effects on people presenting chronic obstructive pulmonary disease (COPD) or asthma attacks than others (Abbey et al., 1993; Goudarzi et al., 2012). Finally, the WHO (2003) officially stated that serious health risks may potentially arise in the world population because of high NO₂ exposure. Therefore, mitigating this primary pollutant is becoming a priority target for policymakers as it raises critical questions about the well-established human activity-health-environment relationship.

WHO (2020c) displayed 48 confirmed deaths and 2269 confirmed cases in France, as of March 12th 2020. Illustrating a sharp increase, the "Situation Report" n° 209 indicated 30,277 confirmed deaths and 202,118 confirmed cases, as of August 16th 2020 (WHO, 2020b). At the city level, observing the adequate data suggests that confirmed deaths followed a similar trend over the March 18th-April 27th 2020 period: from 14 to 1387 in Paris; from 0 to 481 in Lyon; from 4 to 381 in Marseille. Since the ongoing COVID-19 crisis is currently far from being solved, several questions remain unanswered. Upon them, what is the role played by ambient pollution on COVID-19-related deaths? According to Ogen (2020), several early studies identified the risk factors that can be associated with the development of the COVID-19 disease: older age (Wu et al., 2020); hypertension (Chen et al., 2020); and smoking (Liu et al., 2020). However, the air pollution factor remains less investigated despite the well-known long-run incidence of fine particles on health. Since countries experienced contrasted rate of COVID-19 diffusion, one should relevantly ask whether atmospheric pollution can complement the population density in driving the spread of the epidemic in urban

areas (Contini and Costabile, 2020). The underlying hypothesis is that a pre-determined NO₂ concentration can foster COVID-19 and make the respiratory system more susceptible to this infection. Demonstrating that NO₂ is a non-negligible driver of COVID-19-related deaths could partially explain the efficiency of past and ongoing lockdown measures while providing evidence on the role of atmospheric co-factors (i.e., the polluting particles linked to fossil energy combustion by transport notably) in spreading the epidemic. Bringing inclusive knowledge on this topic is of high importance as it would help policymakers to manage this health issue more efficiently. Such a crucial question has been tackled by a range of seminal studies which focused on various economies and opened a new research area (Wu et al. (2020) on the USA; Yongjian et al. (2020) on China; Travaglio et al. (2020) on England; Setti et al. (2020) on Italy; Conticini et al. (2020) and Putrino et al. (2020) on Italy). While most of these investigations concluded on the existence of significant interactions between air pollution and COVID-19 cases or mortality, they corroborated the scientific literature highlighting that the exposure to air pollution impacts the spread of various viral infections more globally (Chen et al., 2010, 2017; Ye et al., 2016; Peng et al., 2020). A second range of empirical studies assessed the NO₂ concentration-COVID-19 nexus (Ogen, 2020; Sasidharan et al., 2020; Yao et al., 2020). Focusing on different countries (United Kingdom, China and 4 European countries, respectively) with various methodologies and at different scales (city, provincial and regional levels), these studies supported the existence of a strong association between NO₂ concentration and COVID-19 transmission. Nonetheless, as reminded by Chudnovsky (2020), some criticism toward the conclusions that can be drawn from this type of experiment may remain. Therefore, careful interpretation needs to follow on each step of the empirical procedure. Finally, to the best of our knowledge, no investigation has been conducted on the single French case so far, even though French cities have experienced and are still going through a dramatic COVID-19 crisis.

This research presents at least three novelty aspects. The study provides the first empirical assessment on the relationship between ambient NO₂ concentrations and COVID-19-related mortality in France. To do so, we constructed an original dataset on NO₂ and COVID-19-related deaths over the most available period from March 18th to April 27th 2020 representing 41 consecutive days of observation for three major French cities (Paris, Lyon and Marseille). Second, this study represents the first empirical estimate of threshold levels of NO₂ related to the COVID-19 epidemic. The findings predict the average concentration amount of NO₂ capable of inducing adverse COVID-19-related deaths in urban areas. Finally, this research follows the strategy adopted by a promising air pollution-virus epidemic literature (Alimadadi et al., 2020; Barstugan et al., 2020; Punnett et al., 2020; Randhawa et al., 2020; Tuli et al., 2020), by applying Artificial Neural Networks (ANNs) experiments based on a Machine Learning (ML) approach. A Causal Direction from Dependency (D2C) algorithm is further performed to check the robustness of the estimates, followed by an AUROC test for a diagnosis purpose. Besides bringing high information value for policy purposes, this assessment is believed to bring robust inference able to complement the literature with inclusive knowledge on the COVID-19 topic.

The paper is organized as follows: Section 2 presents a review of the literature. Section 3 displays the data and the methodology applied. Section 4 presents the empirical results. Section 5 conducts a discussion on our findings. Section 6 concludes and gives policy recommendations.

2. Literature review

Investigations of the relationship between air pollution and COVID-19 has attracted a range of analyses conducted through various approaches. This section aims at summarising the literature outlining the overall impact of air pollution and specifically NO₂ on COVID-19 related mortality. Table 1 outlines the main information on this literature. Studies are outlined in an orderly manner (i.e., by order of appearance in the Section).

¹ As relevantly mentioned in Anjum (2020), 9% of global death can be attributed to air pollution for the year 2017. This is equivalent to 7 million premature deaths. Therefore, air pollution is now recognized as one of the world's important deaths drivers (after high blood pressure, smoking and high blood sugar) (Ritchie and Roser, 2019).

Table 1
Previous air pollution-COVID-19 assessments.

Author(s)	Country	Sample period	Air pollution variable(s)	Evidence on the effect of air pollution on COVID-19 lethality
Studies on Multi-pollutants:				
Wu et al. (2020)	3087 counties in the USA	Up to April 22nd 2020	PM _{2.5}	Yes
Yongjian et al. (2020)	120 cities in China	January 23rd 2020–February 29th 2020,	PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ and O ₃	Yes
Pansini and Fornacca (2020)	on China, Iran, Italy, Spain, France, Germany, UK, and the USA	March 2020–April 2020	PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ and O ₃	Yes
Travaglio et al. (2020)	120 sites in England	February 1st 2020–April 8th 2020	NO ₂ , NO _x and O ₃	Yes
Setti et al. (2020)	8 Italian regions	February 10, 2020–February 29, 2020,	PM ₁₀	Yes
Conticini et al. (2020)	Northern Italy	March 15th 2020 onward	PM ₁₀ , PM _{2.5} , O ₃ , SO ₂ and NO ₂	Yes
Sasidharan et al. (2020)	London (UK)	data up to March 31st 2020	PM _{2.5} , NO ₂	Yes
Zoran et al. (2020)	Milan (Italy)	January 2020–April 2020	NO ₂ and O ₃	Yes
Bashir et al. (2020)	California (US)	March 4, 2020–April 24, 2020	PM _{2.5} , PM ₁₀ , SO ₂ , NO ₂ , Pb, VOC, and CO	Yes
Saez et al. (2020)	Catalonia (Spain)	February 25th 2020–May 16th 2020	NO ₂ and to PM ₁₀	Yes
Fattorini and Regoli (2020)	71 Italian Provinces	Data up to April 27th 2020	PM _{2.5} , PM ₁₀ and NO ₂	Yes
Vasquez-Apestegui et al. (2020)	24 districts of Lima (Perù)	Data up to June 12th 2020	PM _{2.5}	Yes
Frontera et al. (2020)	Italian regions	Data up to March 31, 2020	PM _{2.5}	Yes
Yao et al. (2020)	Wuhan (China)	January 19th 2020–March 15th 2020	PM ₁₀ and PM _{2.5}	Yes
Razzaq et al. (2020)	10 US States	February 29th 2020–July 10th 2020	O ₃	Yes
Magazzino et al. (2020c)	3 French cities	March 18th 2020–April 27th 2020	PM _{2.5} and PM ₁₀ ,	Yes
Assessments on the single effect of NO₂:				
Chakraborty et al. (2020)	18 Indian States	June 8th 2020–June 15th 2020	NO ₂	Yes
Filippini et al. (2020)	28 provinces (Northern Italy)	February 1st 2020–April 5th 2020	NO ₂	Yes
Yao et al. (2020)	63 Chinese cities	January 1st, 2020–February 8th, 2020	NO ₂	Yes
Ogen (2020)	66 administrative regions belonging to four European countries (Italy, Spain, France, and Germany)	January 2020–February 2020	NO ₂	Yes

Notes: “Yes” means that the existence of a significant association between air pollution levels and COVID-19 cases/mortality is established.

Source: our elaborations.

Wu et al. (2020) identified the pre-existing conditions that increase the risk of death due to COVID-19. They examined whether long-term exposure to PM_{2.5} can be associated with an increased COVID-19 fatality in the US. Having collected data from 3000 counties up to April 22nd 2020, they applied a negative binomial mixed model. Controlling for population size, age, and weather, findings suggested that an increase of only 1 µg/m³ in PM_{2.5} is associated with 8% rise in the COVID-19 death rates. Subsequently, Yongjian et al. (2020) assessed the air pollution-COVID-19 nexus in China by compiling data on 120 cities from January 23rd to February 29th 2020. The authors employed a Generalized Additive Model (GAM) on six air pollutants (PM_{2.5}, PM₁₀, SO₂, CO, NO₂ and O₃) merged with a COVID-19 confirmed cases database. Statistical outputs allowed the authors to attest the existence of a positive and significant association between PM_{2.5}, PM₁₀, NO₂ and O₃ concentrations with COVID-19 confirmed cases in China. More precisely, a 10-µg/m³ rise in PM_{2.5}, PM₁₀, NO₂ and O₃ is linked with a 2.24%, 1.76%, 6.94% and 4.76%, increase in daily COVID-19 cases, respectively. Pansini and Fornacca (2020) examined the geographical character of COVID-19 and whether its spreading is correlated with air pollution concentration measured with satellite. Their focus was on China, Iran, Italy, Spain, France, Germany, UK and the USA. More viral infections have been recorded in the areas where PM_{2.5} and NO₂ values are critical. Travaglio et al. (2020) demonstrated that NO_x and SO₂ levels are significantly associated with the numbers of deaths from COVID-19 in Great Britain. This corroborates the findings from Setti et al. (2020) who claimed similar evidence for the Italian case, except that the authors considered the number of PM₁₀ daily limit value

exceedances as a potential COVID-19-related deaths driver. As a result, a direct relationship between the number of persons infected by COVID-19 and the PM₁₀ concentration levels in specific areas of Italy was established. Conticini et al. (2020) explored the correlation between the atmospheric pollution and the high level of COVID-19 lethality in Northern Italy. Findings displayed strong evidence in line with the pollution-led-COVID-19 deaths hypothesis. Using data up to March 31st 2020, Sasidharan et al. (2020) conducted a preliminary analysis on short-term NO₂ concentration and COVID-19 cases and fatality rates for the city of London. COVID-19 fatality rate was found to increase with rising short-term NO₂ pollution, confirming a significant correlation among these indicators. Zoran et al. (2020) assessed the relationship between ground levels of O₃ and NO₂ with COVID-19 infections (i.e., total number, daily new positive and total deaths cases) in Milan (Italy). Results claimed evidence that high levels of urban air pollution have a significant impact on SARS-CoV-2 diffusion. Bashir et al. (2020) presented a study on the impact of air pollutants (PM_{2.5}, PM₁₀, SO₂, NO₂, Pb (Lead), VOC (Volatile Organic Compounds), and CO) on the COVID-19 epidemic in California. Findings indicated that environmental pollutants, such as PM₁₀, PM_{2.5}, SO₂, NO₂ and CO have a significant correlation with the COVID-19 epidemic in this US state. Saez et al. (2020) explored the effect of long-term exposure to NO₂ and PM₁₀ as predictors of the spread of COVID-19 in Catalonia (Spain). Results suggested that, although some mechanisms may explain this relationship, the spatial spread of COVID-19 in Catalonia may be attributed to population interactions rather than immune sensitivity due to air pollution. Collecting data on 71 Italian provinces, Fattorini and Regoli (2020) provided

consistent insights on the effect of PM_{2.5}, PM₁₀ and NO₂ exposure on COVID-19 confirmed cases. This is also in line with Vasquez-Apestegui et al. (2020), Frontera et al. (2020) and Yao et al. (2020) as they found evidence supporting the existence of a spatial association between PM_{2.5} and COVID-19 confirmed cases while considering 24 districts of Lima (Perù), Italian regions, and the city of Wuhan (China), respectively. Finally, Razzaq et al. (2020) showed that highly polluted areas display higher intensity of COVID-19 contamination while considering the top 10 affected states of the US. Inversely, the authors highlighted that lockdown measures temporarily decrease air pollution, giving important insights on the possible mechanisms through which the epidemic may have been slowed down.

Only four studies investigated the link between NO₂ and COVID-19 related mortality, as shown in Table 1, where Chakraborty et al. (2020) focused on 18 Indian States, Filippini et al. (2020) on 28 provinces of Northern Italy, Yao et al. (2020) on 63 Chinese cities, Ogen (2020) for 66 administrative regions among four European countries (Italy, Spain, France and Germany).

Chakraborty et al. (2020) attempted to determine the effect of NO₂ concentration on COVID-19 deaths and case fatality rate in 18 Indian States. Empirical results showed that both associations are statistically significant and positive, indicating that homeless, poverty-stricken Indians, roadside vendors and many others who are regularly exposed to vehicular exhaust, may be at a higher risk in the COVID-19 pandemic. Filippini et al. (2020) examined the infection prevalence in the most affected regions in 28 provinces of Northern Italy. They collected NO₂ tropospheric levels using satellite data available at the European Space Agency. As a result, little association of NO₂ levels with SARS-CoV-2 prevalence up to about 130 µmol/m² was supported, while a positive association was evident at higher levels. Using both cross-sectional and longitudinal analyses, Yao et al. (2020) reported a significant relationship among variables, suggesting the ambient NO₂ may seriously contribute to COVID-19 pandemic expansion in the Hubei Province. In addition, Ogen (2020) employed tropospheric concentration of NO₂ measured by satellite (i.e., the Sentinel-5 Precursor space-borne satellite with a spatial resolution of 5.5 km) and COVID-19 fatality cases in 66 administrative regions belonging to four European countries (Italy, Spain, France and Germany). By controlling for the atmospheric condition, the author showed that 78% of fatality cases were in regions displaying the highest NO₂ concentration levels. Thus, regions characterized by high NO₂ concentrations present important correlation with the COVID-19 fatality rates.

In view of these empirical studies, one can follow Zhu et al. (2020) while considering that air quality index may partially mediate the association of human mobility with COVID-19 spread. This literature review highlights three major gaps. First, since the COVID-19 crisis is currently far from being over, the few empirical works brought non-sophisticated results but seminal evidence. Thus, findings remain preliminary and must be subject to careful interpretation. Meanwhile, the ongoing nature of the crisis and the complexity of such topic requires urgent investigations. By referring to the literature, this calls for the use of the most advanced empirical procedures able to overcome the well-known limits of econometrics strategies. Far from being optional, it emerges as necessary in the prospect of bringing robust inferences on this topic. Second, only few studies investigated the air pollution-COVID-19 relationship using a single-pollutant approach. The effect of NO₂ on COVID-19 related mortality has not been explored in sufficient detail in the literature, although NO₂ is one of the most critical air pollutants as a precursor to secondary pollutants, including O₃ and fine particles. Finally, no single assessment has been performed on the relationship for the French cases so far, indicating the existence of a critical gap in the literature. Therefore, the main proposition of this paper is to fill these above-mentioned gaps in a single manner. Hence, this study provides a first and preliminary analysis on the relationship between NO₂ and COVID-19-related deaths for three major French cities (i.e., Paris, Lyon, and Marseille). The analysis is performed using

Artificial Neural Networks (ANNs) experiments (Machine Learning) which enable estimating the first threshold values of NO₂ concentrations connected to COVID-19-related deaths. This method is also complemented with a Causal Direction from Dependency (D2C) algorithm to check the consistency of the findings.

3. Methods

3.1. Data collection

To assess the relationship between NO₂ concentration and COVID-19 fatality in France, daily data at city level were collected. Data on confirmed deaths (total and daily), resuscitations (daily), and hospitalizations (daily) due to COVID-19 were collected for each selected department: Paris (the Paris department), Marseille (the Bouches du Rhône department), Lyon (the Rhône department). Data were then compiled using the French National Public Health Agency's reports and updated with daily frequency.

NO₂ concentration levels (expressed in µg/m³) were compiled for the three French cities (French National Institute of Statistics and Information about the Economy, INSEE, 2020). For each city, the concentration measures given by operating environmental monitoring stations were averaged. Having hourly data for each city, the daily arithmetic average was calculated to obtain an average NO₂ concentration for each day and each city. NO₂ data were collected by the French Federation of Certified Associations for the air quality monitoring. This association federates all air quality monitoring institutes across the French territory. For Paris, NO₂ data were taken from Airfare based on information given by forty environmental monitoring stations. For Marseille, NO₂ data were collected from seven environmental monitoring stations and gathered by AtmoSud. For Lyon, NO₂ data were collected by Atmo Auvergne-Rhône-Alpes which relies on 11 environmental monitoring stations to assess air quality measures.

The data for the COVID-19 mortality rates and NO₂ concentrations for the three French cities were collected for the period from March 18th 2020 to April 27th 2020, which allowed examination of the evolution of both indicators along forty-one consecutive days for each city. The choice of the starting period was constrained by COVID-19 data availability because the French National Public Health Agency (Santé Publique France) began to publish public daily estimations of COVID-19 expansion (deaths) for each department from March 18th 2020 onwards.

3.2. Model construction

The model was constructed using ANNs techniques in an ML context with Oryx 2.8.0 protocol software. The main objective of this work is to define a model capable of carrying out a predictive analysis of the quantity of NO₂ that assists the spread of COVID-19 deaths. To carry out the experiments on the three selected French cities, ANNs defined through a series of experimental tests were built. A combination of four variables was used (Table 2), with also the mathematical transforms of all variables in the first differences (*d*), and the logarithmic transforms (*ln*).

The model requires appropriate selection and preparation of input data and the structure of the network. Unlike econometric models, the ANNs do not have the problems of stationarity and have different operating logic. In ANNs the variables need to be converted to

Table 2
List of variables.

Deaths	Data on confirmed deaths
Hosp	Hospitalizations
NO2	NO ₂ concentrations levels (expressed in µg/m ³)
Resusc	Resuscitations

dimensionless values. In the next step, the weights of the variables were normalized to ensure they are not influenced by the absolute value of the variable where the variables with a higher total value are more influential than others with a lower value. For this reason, the architecture of the constructed networks was not limited to a single intermediate layer, as stated by Gareta et al. (2006), and Singhal and Swarup (2011). In this work, the proposal of Wanas et al. (1999) was followed, who recommended that the optimal number of nodes in the intermediate layer, which allows the network to obtain the best performance, is equal to the logarithm of the number of sample data used to estimate the network.

Although there are numerous approaches and algorithms for using NN, according to White (1988) the Multilayer Perceptron approach with ANNs experiment was applied in this study. Starting by the perceptron, the method applies a network with m of neurons. If d is the number of inputs, the output will be the target:

$$y_j = y \left(\sum_{i=0}^d w_{ji} x_i \right) \quad [1]$$

where x_i are the inputs, w_{ji} are the weights of each input combined with each output, and y_j is the target. With this architecture, we use the activation functions of the threshold function type. Therefore, the final outputs of the network are verifiable by the following expression:

$$z_k = z \left(\sum_{j=0}^m w'_{kj} y_j \right) \quad [2]$$

where z_k is the final output, w'_{kj} are the weights for each processing unit, and y_j is the signal sent by the hidden units. The bias, as a coefficient respectively of the input x_0 and y_0 , has been calculated by setting them equal to 1. Then, combining the above equations, we can write the final result:

$$z_k = z \left(\sum_{j=0}^m w'_{kj} y \left(\sum_{i=0}^d w_{ji} x_i \right) \right) \quad [3]$$

To carry out the experiments on the three selected French cities, we built ANNs defined through a series of experimental tests. The training of the network takes place by providing a series of precise indications regarding the type of algorithm and recommended training. In particular, the difficulty in framing the best architecture of the NN is to find the balance between the “Scaling Method” and the “Unscaling Method”. Thus, a combination that minimizes errors concerning the number of layers activated by hyperbolic activation functions was selected. Next, tests were carried out to optimize the algorithm selected by the machine. Through these tests, we analyzed how long it takes (epochs) for the predictive error of estimate to decrease until it reaches a value close to zero. The analysis proceeds through the performance of the “selection order” about the neurons used by the NN, and the distribution of data was verified on the predictive regression line. Finally, the so-called cutting technique was used to estimate the point in the neural transmission from the inputs to the target where the predictive concentrations of NO₂ leading to an increase in the number of deaths due to COVID-19 were identified.

Table 3 describes the steps followed in the methods section for the use of NNs in AD-Designer, Python or R to estimate the concentration of NO₂.

4. Results

4.1. Aggregate results

Fig. 1 represents the summary of the dataset used in our ANNs. In total, nine variables were used, of which six represent the input process, and three are the generated target. In Fig. 2, the behaviour of the instances are presented using a pie chart elaborated by the used protocol.

Table 3

ANNs experiment procedure.

[1] ANNs METHOD	Experiment	
Scaling layer	Mean and Standard Deviation	
Perceptron layers	Hyperbolic Tangent	
Unscaling layer	Minimum-Maximum	
Bounding layer	Apply - Target (Deaths)	
[2] TRAINING STRATEGY	Experiment	Type
A loss index	Normalized squared error	L2 regularization method
An optimization algorithm	Quasi-Newton method	Very High
[3] MODEL SELECTION	Experiment	
Order selection	Incremental order algorithm	
[4] TESTING ANALYSIS	Experiment	Type
Sunburst ML	Expected Error	Node threshold: 512

As observed from Fig. 2, the instances of the ML process were equal to 41. Those representing the training are 25 (60.9%). This result underlines how, compared to a choice of n projects, the model selected 25 out of 41 potential models to best suit the target. As for the testing instances, there were eight instances (19%). This value represents the result of the choice of numerous training models. Since it is the same and never less than the selection instances, this reinforces the previous findings. Finally, the number of unused instances is zero (0%). Overall, the result confirms the goodness of the model. No anomalous values, which would have invalidated the results were generated. To evaluate the quality of the model and the architectural construction of the NN, Table 4 presents the results of five tests, which are the most used in the analysis of NNs and outlines the model error test. This task measures all the errors of the model taking into account every used instance and model evaluation for each use. The training, selection and testing test all have errors of less than 10%, which confirms the construction and the goodness of the applied neural network.

After observing the behaviour of the datasets concerning the processing in ML of the algorithm, the result of the ANN is analyzed in Fig. 3.

Fig. 3 is the result of the graphic elaboration of the NN generated in Oryx with Designer extension version 1.8. It contains a scaling layer, an NN, and an unscaling layer. The yellow circles represent the scaling neurons, the blue circles the perceptron neurons, the red circles the unscaling neurons, and the purple circles the bounding neurons. The number of inputs is 9, while there are 3 outputs and bounding neurons. The complexity, represented by the numbers of hidden neurons, is 10:7:6:1. Therefore, a complex NN characterised by 3 targets (*Deaths*, *Hosp*, and *Resusc*) was analyzed in this work. Through the “Importance test” the target was defined that best represents the NN. To facilitate the reading of the results obtained and ensure their replication by the scientific community, the tests on NN are presented in the Appendix. Below, the estimation experiment on the concentration level NO₂ connected to the deaths during the COVID-19 epidemic in the three French cities is shown. The system used is the “Plot Directional Output”, which is very useful to reveal the variation of outputs as a function of a single input, when all the others are fixed. This can be seen as the cut of the NN model along some input direction and through a reference point.

4.2. Results on Paris²

The “Importance test” was applied to the hyperbolic equations of the ANNs to verify which target receives the most signals from the inputs for

² In Supplementary material: Quasi-Newton method error history; Incremental order error plot; Clear ANNs expression.

Figure 2. Instances pie chart.

Fig. 1. Variable bars chart.

Fig. 2. Instances pie chart.

Table 4
Testing analysis.

	Training	Selection	Testing
Sum squared error	0.0066	0.0059	0.0098
Mean squared error	0.005	0.0041	0.0034
Root mean squared error	0.0015	0.0012	0.001
Normalized squared error	0.0016	0.0031	0.0081
Minkowski error	0.0014	0.0027	0.0017

Paris (Fig. 4).

The results obtained advised that NN should be limited to the “Deaths” Target (88.9), in which case the “Target Selection Algorithm” on ANNs was applied. By selecting two different models (Input Selection Algorithm and Target Selection Algorithm), the final architecture of the

NN for the city of Paris, shown in Fig. 5, was built.

The ANNs in Fig. 5 show the number of inputs, outputs and bounding neurons are all 1. The complexity, represented by the number of hidden neurons, is 10:7:6:1. A standard method to test the loss of the model is to perform a predictive linear regression analysis between the scaled neural network outputs and the corresponding targets for an independent testing subset (Fig. 6).

As seen from Fig. 6, the prediction line (with respect to the target, Deaths) confirms the goodness of the elaboration of the algorithm on the final architecture. Therefore, the “Plot Directional Output” option was used in order to obtain the signal threshold value from NO₂ to the target (Fig. 7).

Fig. 7 shows the result of the first experiment. The cut-off signal in ANNs transmission from NO₂ input to the target Deaths has been precisely identified and corresponds to the value of 22.6 µg/m.³ This value

Fig. 3. ANNs results.

represents the threshold value for Paris, and it may be able to convey COVID-19 or accelerate its adverse health effects.

4.3. Results on Lyon³

The “Importance test” on the hyperbolic equations of the ANNs to verify which target receives the most signals from the inputs was also used for the city of Lyon (Fig. 8).

The results in Fig. 8 confirm that for Lyon the target most influenced by the Inputs is *Deaths*. The two selected models used for Paris were also applied to generate the new architecture of the NN for Lyon. Through hyperbolic transformations, the model redesigned the best NN capable of representing the effect of the input on the final target. Thus, the final architecture of the NN for the city of Lyon was constructed as presented in Fig. 9.

The new ANNs in Fig. 9 present a number of inputs of 1, and the number of outputs and bounding neurons at 1. The complexity, represented by the numbers of hidden neurons, is 10:7:6:1. Through the use of the Predictive Linear Regression test, the goodness of the latest constructed NN was verified and presented in Fig. 10 demonstrating high functional relationship between the signals in the NN.

The “Plot Directional Output” was then used in order to obtain the signal threshold value from NO₂ to the target (Fig. 11).

Fig. 11 shows the result of the experiment in Lyon. The cut-off signal in ANNs transmission from NO_2 input to the target *Deaths* has been

Fig. 4. Importance test on Paris.

identified as 15.9 $\mu\text{g}/\text{m}^3$.³ The value obtained represents the concentration of NO_2 able to exacerbate the number of deaths caused by COVID-19 in the city of Lyon, which was even smaller than the threshold identified for Paris.

4.4. Results on Marseille⁴

Compared to Paris and Lyon, Marseille has a much lower population density of 3600/km². The study of the effect of NO₂ on this city

Fig. 5. ANNs selection results for the city of Paris.

Fig. 6. Predictive Linear Regression test.

³ In Supplementary material: Quasi-Newton method error history; Incremental order error plot; Clear ANNs expression.

⁴ In Supplementary material: Quasi-Newton method error history; Incremental order error plot; Clear ANNs expression.

Fig. 7. Deaths- NO₂ directional output.

Fig. 8. Importance test on Lyon.

concerning COVID-19 deaths can help understand if, with a greater or lesser concentration of people, the results of NO₂ are different. The “Importance test” was applied to the hyperbolic equations of the ANNs to verify which target receives the most signals from the inputs for Marseille (Fig. 12).

The results in the Fig. 12 confirm that for Marseille, the target most influenced by the Inputs is *Deaths*. In particular, it can be observed how the target (*Deaths*) compared to Paris and Lyon is almost close to 100%. This result suggests the hypothesis that during the COVID-19 pandemic, the inputs used in the NN in Fig. 2 transmit a strong hyperbolic signal to the target (*Deaths*). By selecting two different models (Input Selection Algorithm and Target Selection Algorithm), we proceed to build the final architecture of the NN for Marseille (Fig. 13).

The architecture of the NN generated by the selection of the inputs and the target presents a different functionality compared to Paris and Lyon. The number of inputs is 1, and the number of outputs and bounding neurons is 1. The complexity, represented by the numbers of hidden neurons, is 8:5:3:5. In particular, we can see how at hidden layer 4, the number of neurons increases to 5, which makes the analysis of the

Fig. 9. ANNs selection results for the city of Lyon.

Fig. 10. Predictive Linear Regression test.

Fig. 11. Deaths- NO₂ directional output.

Fig. 12. Importance test on Marseille.

signals towards the target much more complicated. Through the use of the Predictive Linear Regression test, the goodness of the latest constructed NN was verified and presented in Fig. 14.

As seen in Fig. 14, the straight line has a smaller distance, on the ordinate axis, from all points of the diagram to the predicted and real values. Therefore, the predicted and real variables of the study (concerning Target) have a linear relationship between them. Thus, the points of the scatter plot tend to arrange themselves in a straight line. The “Plot Directional Output” was therefore used for Marseille to obtain the signal threshold value from NO₂ to the target. The final architecture of the NN obtained in Fig. 13 and the presence of interruption and reopening between the neurons that compose the NN concerning the target, undoubtedly generate a very different cut signal path compared to that obtained for Paris and Lyon. The complexity of the input-target NN hides within its numerous information that may be useful to understand the specific effect of NO₂ concentrations on COVID-19 deaths.

Fig. 15 shows the result of the experiment for Marseille. As expected, the signal has five inflection points, higher in number than those present

Fig. 13. ANNs selection results for Marseille.

Fig. 14. Predictive Linear Regression test.

for Paris and Lyon. The cut-off signal in ANNs transmission from NO₂ input to the target *Deaths* has been identified as 21.8 µg/m³,³ which is close to that of Paris and higher than Lyon. This result could be explained by the more significant impact that NO₂ can have even on a city with low population density in a virus pandemic situation. Given the winter period, the elective proximity to the sea with higher UV emissions (average annual UV index: Marseille 5, Paris 2, Lyon 3) did not help in reduction of NO₂. In fact, under the influence of UV radiation, NO₂ decomposes into ozone. Strong emissions of nitrogen oxides, therefore, lead both to NO₂ pollution and also to ozone. Due to the higher UV radiation and higher temperatures, NO₂ is transformed more quickly into ozone in summer.

5. Robustness checks

The results obtained through ANNs are tested through a three-stage predictive causation algorithm (D3S), which can be interpreted as a

Fig. 15. Deaths- NO₂ directional output.

Table 5

Causality predicted NO₂ on Death (Paris).

Application scenario 1 (100 repetitions)				
	AVG.ScS	AVG.peak	AVG.CPU time	
	Scsum	Scspec	e-c ratio	reduction%
NO ₂	0.98	0.90	68.55%	40%
hidden	0.93	0.70	3.10%	81.66%

Table 6

Causality predicted NO₂ on Death (Lyon).

Application scenario 2 (100 repetitions)				
	AVG.ScS	AVG.peak	AVG.CPU time	
	Scsum	Scspec	e-c ratio	reduction%
NO ₂	0.97	0.92	77.45%	38%
hidden	0.81	0.30	8.5%	91.16%

derivation of the D2C algorithm already used by Magazzino et al. (2020a; 2020b), and Mele and Magazzino (2020a; 2020b). The algorithm adapted from the previous programming simulated 4 scenarios concerning three stages of ML: “AVG.ScS”, “AVG.peak”, “AVG.CPU time”. Three scenarios are real by analyzing the data of the three French cities under study. The last scenario (4) represents a random hypothetical scenario in which the algorithm assumes another estimate for another city not present in the dataset. This experiment is useful for understanding the action of the ML process in an aggregate data environment.

Following the results obtained from the neural network, the variable “Death” was used as a target for each scenario. Tables 5–7 show the link between NO₂ emissions concerning the “Death” target for Paris, Lyon and Marseille. The three stages of ML analysis are consistent for each analyzed city. The subset of AVG.ScS composed of Scsum and Scspec shows that the Scsum values for each city are more significant than hypothetical unknown values that could alter the analysis. The values of the Scspec, which represent the causal links of sub-descriptors, are more significant for NO₂ than the hidden values. Also, the value of the e-c ratio relative to the AVG peak stage shows higher values of NO₂ for each city concerning situations hidden from the analysis that would distort the result. Finally, the analysis considers the AVG.CPU time stage and the percent reduction value. This stage is critical in ML analysis as it represents the processing speed of the system in estimating the predictive causal links between the input and the target. As seen, it is lower than the self-generated hidden input for each city considered. Since the lower the computation time percentage and the higher the probability that the event is correct, this is another validation that the model found predictive causal links between NO₂ and Death. Besides, Table 8 represents a hypothetical situation different from the considered cities, where the presence of errors at each stage confirms that the algorithm did not undergo distortion when it analyzed the predictive causal relationships for Paris, Lyon and Marseille.

6. Discussion

6.1. Summary of results and interpretations

Table 9 summarizes the results obtained by the ML model with ANNs. In quantitative terms, the excess risk reported compared to our

Table 7

Causality predicted NO₂ on Death (Marseille).

Application scenario 3 (100 repetitions)				
	AVG.ScS	AVG.peak	AVG.CPU time	
	Scsum	Scspec	e-c ratio	reduction%
NO ₂	0.96	0.98	79.18%	47%
hidden	0.77	0.60	5.19%	93.13%

Table 8Causality predicted NO₂ on Death (random).

Application scenario 4 (100 repetitions)				
	AVG.ScS	AVG.peak	AVG.CPU time	
	Scsum	Scspec	e-c ratio	reduction%
NO₂	0.31	0.12	0.51%	98%
hidden	0.10	0.15	0.74%	97%

Table 9Summary deaths- NO₂ directional output.

City	Population density	NO ₂ µg/m ³ (threshold)
Paris	21,616/km ²	22.9
Lyon	11,000/km ²	15.8
Marseille	3600/km ²	21.8

values is dramatic. In the city of Paris, an increase in NO₂ concentration beyond the 22.9 µg/m³ threshold could generate an increase in mortality (in a COVID-19 pandemic). For Lyon, on the other hand, any value above 15.8 µg/m³ in NO₂ would generate an increase in deaths. Finally, for Marseille, an increase in NO₂ concentrations above 21.8 µg/m³ would generate an increase in mortality.

All the threshold values discovered are lower than the limits imposed by Directive 2008/50/EC of the European Parliament of 40 µg/m³.³ These findings are important in a COVID-19 pandemic situation. It is very likely that the relationship between NO₂ and Covid-19 induced mortality is indirect. High concentrations of NO₂ lead to manifestations of inflammation of the respiratory tract and worsening of irritations in general; less resistance to infections; heart rhythm disturbances and heart attacks, increased hospitalizations following lung disease, and a higher rate of mortality, caused by disorders of the circulation and respiratory tract. These adverse human health effects at NO₂ exposures correspond to the COVID-19 effects that cause death. COVID-19 and the resulting disease, interstitial pneumonia has been defined, characterized by a robust inflammatory process in the space between the alveoli where the exchange takes place between oxygen (necessary to maintain vital functions) and carbon dioxide (waste product breathing). What follows is an alteration of the physiological conditions. In particular, COVID-19 also determines a rapid and significant increase in the inflammatory response, which can involve the blood vessels and the heart. This situation increases the risk of events, such as vasculitis and myocarditis. In the presence of cardiac arrhythmias, this situation generates a heart attack and death (Inciardi et al., 2020). The result presented in this work could also interpret other similar works, such as that obtained by Ogen (2020) who concluded that high concentrations of NO₂ could be associated with a high number of deaths for COVID-19. However, this research is only an initial indication of a correlation between the level of air pollution, the movement of air, and the severity of the course of coronavirus epidemics. The result of our study is different from the one mentioned. We have found a precise quantity of NO₂ that can increase the probability of death in a COVID-19 context in which the three French cities serve as study samples. In particular, the study is relevant to all other cities with a population density similar to the three French cities with NO₂ concentrations above the new thresholds identified in this study.

7. Conclusions

This study analyzed the relationship between NO₂ and deaths from COVID-19 in three French cities. Through the use of an experiment in ML with ANNs, we estimated the threshold value of NO₂ beyond which the number of deaths in the presence of COVID-19 would increase. The study takes into account the adverse health effects of the particulate objects of the study. Even in the absence of a pandemic situation, high concentrations of NO₂ generate adverse effects and danger to human

health. Dry deposition of NO₂ can be inhaled, reaching the deepest part of the human respiratory system. The finer fractions could filter even deeper into the body by travelling into the blood and reaching the cells. Previous studies affirm a correlation between air pollution and the spread of COVID-19. Starting from these hypotheses, the current study verified the possibility of determining threshold values of NO₂ which correspond to the optimal value for adverse effect of coronavirus. The study found that if the signal from the NN (from input to output) is cut to a precise amount, there is a reduction in the number of coronavirus deaths in the three French cities studied. This result suggests that there are certain conditions which increase the likelihood of the spread and aggravation of the disease. The three cities taken as a statistical sample in this study have different population densities. We found that threshold values of NO₂ connected to COVID-19 ranged between 15.8 µg/m³ for Lyon, 21.8 µg/m³ for Marseille and 22.9 µg/m³ for Paris.

This result is relevant to any city with a population density similar to the studied in this work. The objective of the work is to identify potential threshold values relevant to environmental intervention policies aimed at limiting the concentrations of NO₂ in the new pandemic situation. Pending further scientific confirmation, our threshold value could be considered a possible indirect indicator of the virulence of the COVID-19 epidemic.

CRedit author statement

Marco Mele, Conceptualization, Methodology, Resources, Software, Cosimo Magazzino, Investigation, Formal analysis, Data curation, Software, Nicolas Schneider, Data curation, Writing – original draft. Vladimir Strezov, Data curation, Writing – original draft.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envres.2020.110663>.

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