Links between air pollution and COVID-19 in England

Marco Travaglio [1], Rebeka Popovic [1], Yizhou Yu [1], Nuno Santos Leal [1], Luis Miguel Martins [1]

[1] MRC Toxicology Unit, University of Cambridge

Correspondence to: L. Miguel Martins, Cell Death Regulation Laboratory, MRC Toxicology Unit, e-mail: martins.lmiguel@gmail.com

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ABSTRACT

In December 2019 a novel disease coronavirus disease 19 (COVID-19) emerged in the Wuhan province of the People's Republic of China. COVID-19 is caused by a novel coronavirus (SARS-CoV-2) thought to have jumped species, from another mammal to humans. A pandemic caused by this virus is running rampant throughout the world. Thousands of cases of COVID-19 are reported in England and over 10,000 patients have died. Whilst there has been progress in managing this disease, it is not clear which factors, besides age, affect the severity and mortality of COVID-19. A recent analysis of COVID-19 in Italy identified links between air pollution and death rates. Here, we explored the correlation between three major air pollutants linked to fossil fuels and SARS-CoV-2 lethality in England. We compare up-to-date, real-time SARS-CoV-2 cases and death measurements from public databases to air pollution data monitored across over 120 sites in different regions. We found that the levels of some markers of poor air quality, nitrogen oxides and ozone, are associated with COVID-19 lethality in different English regions. We conclude that the levels of some air pollutants are linked to COVID-19 cases and morbidity. We suggest that our study provides a useful framework to guide health policy in countries affected by this pandemic.

Keywords: SARS-CoV-2; COVID-19; Air pollution; Nitrogen oxides, Ozone, lethality.

Abbreviations: SARS, severe acute respiratory syndrome

INTRODUCTION

In December 2019, a high number of pneumonia cases of unknown cause were detected in Wuhan, province of Hubei, China. A molecular analysis from affected patients revealed that their symptoms were caused by an infection by a novel coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogenic agent of coronavirus disease 19 (COVID-19) [1]. Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and classified within the Nidovirales order [2]. Similar to previous epidemics of novel coronavirus diseases, SARS-CoV-2 causes SARS which ultimately can lead to respiratory failure and death [2]. While the initial symptoms of COVID-19 include fever, with or without respiratory syndrome, a crescendo of pulmonary abnormalities develop later in patients[3]. Recent studies show that most patients only present mild illnesses, but approximately 25% of hospital-admitted cases require intensive care treatment because of viral pneumonia with respiratory complications [4].

Whilst abundant research into the pathogenesis of COVID-19 suggests that this disease likely stems from an excessive inflammatory response [5], the exact predisposing factors, contributing to increased clinical severity and death in patients remain unclear. Moreover, the risks associated with COVID-19 are unknown. Previous studies suggested that individuals over the age of 60 or with underlying health conditions, including cardiovascular disease, diabetes, chronic respiratory disease and cancer, are at highest risk of severe disease and death (Verity et al., 2020). Long-term exposure to air pollutants has been shown as a risk factor mediating the pathogenesis of these health conditions [6].

In fact, prolonged exposure to common road transport pollutants, including nitrogen oxides (NOx), and ground level ozone, a by-product of chemical reactions between NOx and volatile organic compounds, can significantly exacerbate cardiovascular morbidity, airway oxidative stress and asthma [7]. Such pollutants can also cause a persistent inflammatory response and increase the risk of infection by viruses that target the respiratory tract.[8,9]. We therefore addressed whether the infectivity and death rates of COVID-19 in England is linked to air pollution.

This hypothesis is supported by observations that the geographical pattern of COVID-19 propagation and lethality among countries, and even among regions of the same country, closely recapitulates local levels of air pollutants [9]. For example, increased contagiousness and COVID-19 related mortality in Northern Italian regions, including Lombardia, Veneto and Emilia Romagna, correlate with high levels of air pollutants in these regions [9]. These

findings suggest that individuals exposed to chronic high levels of air pollutants may display increased susceptibility to SARS-CoV-2 infection because of compromised immune system defence responses.

Here, we explored the relationship between air pollution and SARS-CoV-2 lethality in England and show an association between airborne toxins released by fossil fuels and the susceptibility to viral infection by SARS-CoV-2 and COVID-19 mortality rates in England.

RESULTS

We analysed the data on total COVID-19 cases and deaths, against the levels of three major air pollutants, collected between the years 2018 and 2019, when no COVID-19 case was reported. Our study used publicly available data from seven regions in England, where a minimum of 2,000 SARS-CoV-2 infections and 200 deaths are reported in the period from February to the 8th of April 2020.

The largest number of COVID-19 deaths in England occurred across London and the Midlands. This spatial pattern in COVID-19 deaths appears to mimic the geographical distribution of COVID-19 related cases (Figure 1). Previous studies suggested that the annual average of nitrogen dioxide concentrations ($\mu g\ m^{-3}$) are largest in these two regions [10]. To investigate whether increased levels of nitrogen dioxide is implicated in COVID-19 infection and mortality, we compared the annual average of daily nitrogen dioxide levels to the total number of COVID-19 cases in each region and found these to be positively correlated (Figure 2B). Our results provide the first evidence that SARS-CoV-2 case fatality is associated with increased nitrogen dioxide levels in England.

We also tested if nitrogen oxide levels are also associated with SARS-CoV-2 case fatality in England. Similar to before, we compared the annual average of daily levels of this pollutant to the total number of COVID-19 cases. Previous studies have shown that high levels of nitrogen oxide are strongly associated with an array of lung diseases, including lung cancer [11]. Similar to nitrogen dioxide exposure, nitrogen oxide concentration positively correlates with both the number of COVID-19 cases (Figure 2B) and deaths (Figure 2A) in England. When comparing the distribution between nitrogen oxide and nitrogen dioxide we observed a similar spatial pattern, whereby London, Midlands and North West show the largest concentration of these air pollutants, with Southern regions displaying the lowest levels in the country (Figure 1). SARS-CoV-2 case fatality followed a similar trend, suggesting a potential link between nitrogen oxide exposure and COVID-19 disease severity in the population of England (Figure 2A).

The correlation between nitrogen dioxide and COVID-19 cases and deaths failed to achieve significance due to data skewness caused by the London Marylebone nitrogen dioxide levels (Supplementary Table 1). To account for this skewness, we applied a negative binomial model to this data. This allowed us to model the skewness of the distribution, and re-assess if nitrogen dioxide could be a predictor of COVID-19 using this alternative statistical model. Using this model, we observed that the coefficient of nitrogen dioxide levels was 0.06032 (standard error= 0.02229, z-value = 2.705, p value = 0.00682), confirming a positive relationship between nitrogen dioxide level and COVID-19 related lethality.

Finally, we investigated whether ground-level ozone is also linked with the spatial distribution of COVID-19 cases and deaths across the country. We found a consistent inverse association between ozone ambient levels and the number of COVID-19 cases in each region (Figure 2B). Similarly, the number of COVID-19 deaths is negatively correlated with levels of ozone across England (Figure 2A). Therefore, our results show that reduced ozone levels are associated with higher SARS-CoV-2 case fatality in England as both COVID-19 cases and deaths are correlated with ozone concentrations.

METHODS

Data sources

The number of SARS-CoV-2 infection cases for each region in England (London, Midlands, North West, North East and Yorkshire, South East, East of England, South West) was obtained from Public Health England (www.gov.uk/government/publications/covid-19-track-coronavirus-cases). Data on SARS-CoV-2 related daily deaths for each region in England were retrieved from the National Health System (www.england.nhs.uk/statistics/statistical-work-areas/covid-19-daily-deaths/). This source includes the most comprehensive region-level repository of COVID-19 deaths in England. The daily deaths summary included deaths of patients who have died in hospitals in England and had tested positive for SARS-CoV-2 at the time of deaths. While this online repository is regularly updated on a daily basis, it is important to note that figures are subject to change due to *post-mortem* confirmation of diagnosis. Furthermore, data do not include deaths outside the hospital and therefore serve as an approximation of the total number of deaths in England. All deaths are recorded against

the date of deaths rather than the day in which the death was announced. The total number of COVID-19 deaths were collected for each region up to and including April 8 2020.

Air pollution data between 2018 and 2019 was obtained from the European Environmental Agency (EEA). This agency offers one of the largest online repositories of up-to-date, quality-controlled environmental information in Europe. For the present study, we collected annual aggregated air quality values (AQ values) determined by the EEA based on primary observations obtained from over 120 monitoring stations across England. Stations located near airports (i.e. Luton) or near/within National Reserves were excluded from the analysis as measured observations are sparse and inconsistent. Because of limited data availability, we also restricted our analysis to individual pollution indices for three major air pollutants, namely nitrogen dioxide, nitrogen oxide and ozone across the pre-specified regions. Nitrogen dioxide, nitrogen oxide and ozone AQ values are expressed in µg/m3 and represent the annual average of daily measurements for each air polluting substance across the year 2018 to 2019 in each specified region. The ID of each monitoring station was matched to each available city by accessing the Department for Environment, Food and Rural Affairs (DEFRA) website. This website contains a resource called DEFRA's Air Quality Spatial Object Register, allowing users to view and retrieve information on the air quality related spatial and non-spatial data objects from the UK's Air Quality e-Reporting data holdings. The annual average of daily measurements for each pollutant in each monitoring area was analysed to determine the influence of toxic exposure on the number of SARS-CoV-2 cases and deaths across England.

Regional heatmaps

Heatmap legends were generated using GraphPad Prism 8(www.graphpad.com) and regions labelled with the mapped colour values.

Statistical Analyses

Data normality was assessed by performing the Shapiro-Wilk test. Correlations were calculated by either the Pearson correlation coefficient, for normally distributed data (nitrogen oxide and ozone) or Spearman correlation coefficient for non-normally distributed data (nitrogen dioxide). The correlation coefficients (R)and p values (two-tailed, 95% interval) are reported. The analysis was performed using GraphPad Prism 8 (www.graphpad.com). A negative binomial model was built to test the significance of tailed-

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distribution (nitrogen dioxide) using the MASS package (www.stats.ox.ac.uk/pub/MASS4/) in R.

DISCUSSION

In this study we identified a positive association between air pollution and SARS-CoV-2 lethality in England, expanding previous evidence linking high mortality rates in Northern Italy with increased toxic exposure to air pollutants [9]. In addition, a new study showed an association between fine particulate matter levels and COVID-19 related deaths in the US by demonstrating that an increase of 1 µg/m^3 of these particulate matter led to an increase of 15% of COVID-19 death rates [6]. Notably, these findings are in line with studies conducted on the previous SARS outbreak, where long-term exposure to air pollutants had a detrimental effect on the prognosis of SARS patients in China [12].

In our study, we found that high levels of two NOx, nitrogen dioxide and nitrogen oxide, correlate with increased COVID-19 mortality and spread in England. NOx gases result from a chemical reaction between nitrogen and oxygen during combustion of fossil fuels and, therefore, represent a significant source of air pollution in areas with high traffic [13]. Previous studies showed that exposure to nitrogen dioxide is associated with a significant decrease in pulmonary function and promotes an inflammatory response in the airway [14] [15] [16]. In fact, a recent study showed that intensive care unit (ICU) ventilation duration associates with pre-admission exposure to nitrogen dioxide[17]. Furthermore, Faustini and colleagues [18] reported that a 10 µg/m3 increase in the annual concentration of nitrogen dioxide is associated with a 13% and 2% increase in cardiovascular and respiratory mortality, respectively. As respiratory and cardiovascular diseases represent potential risk factors associated with increased COVID-19 mortality, our results are in line with the hypothesis that long-term exposure to nitrogen dioxide is linked with increased risk of COVID-19 mortality.

The finding that nitrogen oxide levels positively associate with COVID-19 infection cases and lethality reconciles with previous evidence showing that environmental levels of nitrogen oxide can influence the propagation and severity of other epidemics. Five-year aggregated data of nitrogen oxide levels from both industrialised and rural areas in England indicate that progression of the respiratory syncytial virus (RSV) is directly linked to seasonal variations in nitrogen oxide levels [19]. While the mechanisms by which environmental nitrogen oxide

aggravates the clinical severity of RSV remain unclear, it has been noted that, when inhaled, this gas depresses endogenous production of nitrogen oxide (Hobson and Everard, 2008). Since endogenous nitrogen oxide is known to inhibit RSV replication in the lungs, it has been proposed that exogenous, inhaled nitrogen oxide may trigger RSV replication by repressing production of endogenous nitrogen oxide (Hobson and Everard, 2008). Although a similar mechanism of replication has not been shown for SARS-CoV-2, it is tempting to speculate that this mechanism may account for the observed association between increased ambient nitrogen oxide levels and SARS-CoV-2 lethality. Moreover, nitrogen oxide is a free radical and can be oxidised to nitrogen dioxide, which acts as a pulmonary irritant [20].

In this study, we also reported that increased ozone concentrations are associated with lower COVID-19 risk. Ozone is a secondary by-product of traffic-related air pollution and is generated through sunlight-driven reactions between motor-vehicle emissions and volatile organic compounds [21]. Generally, high ozone levels have been associated with reduced lung function and increased incidence of respiratory symptoms [22]. We found the lowest levels of ozone to be in highly urbanised regions, such London or the Midlands. Given the highly reactive nature of ozone, decreased levels in these regions may indicate increased conversion of ozone to secondary gaseous species, a phenomenon previously reported for areas with increased traffic [23]. For instance, ozone can readily react with other gaseous species and particulates in the environment, resulting in the formation of respiratory irritants, such as terpene derivatives [24]. Therefore, the detrimental effects of low ozone concentration observed in this study could be linked to increased generation of ozone oxidation products. Further research is necessary to determine the exact identity of these pollutants and their effect on COVID-19 severity and progression.

Our results, combined with the recent report from Northern Italy[9], suggest that poor air quality increases the lethality of COVID-19. Future and more detailed studies may further elucidate these observations by addressing potential confounders, including socioeconomic status, comorbidities, age, race, and differences between regional health regulations and their ICU capacities. Nonetheless, our study highlights the importance of continuous implementation of existing air pollution regulations for the protection of human health, both in relation to the COVID-19 pandemic and beyond.

SUPPLEMENTARY DATA

Supplementary Table 1. Air quality values of air pollutants as measured at each monitoring site across England.

Summary of all air quality (AQ) values measured across England and reported to the European Environmental Agency. Data is expressed in $\mu g/m^3$ and indicates the ambient concentration of each pollutant recorded between 2018 and 2019. AQ values from each monitoring station were grouped by region to generate an estimate of the annual average concentration for each pollutant across distinct regions in England.

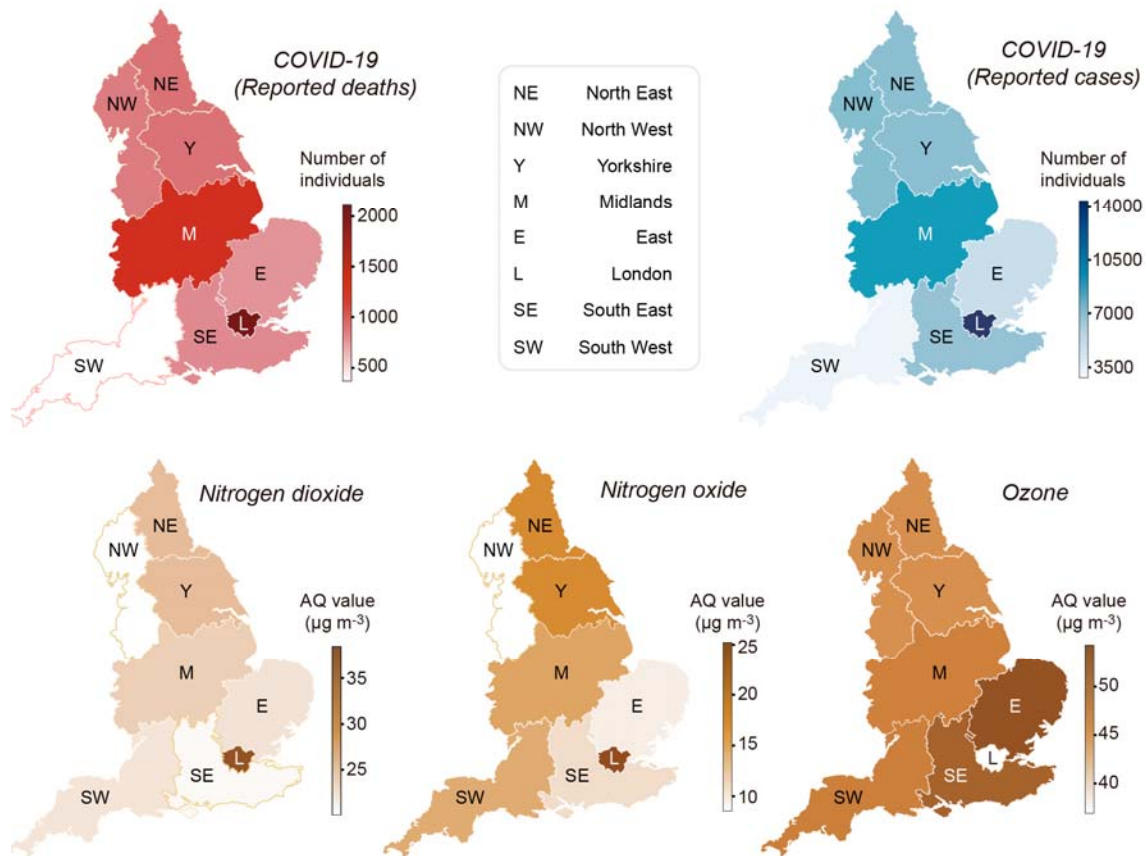**FIGURES & FIGURE LEGENDS**

Figure 1. Regional heatmaps of COVID-19 and pollutants.

The regional English heatmaps of reported deaths and diagnosed COVID-19 cases, up to the 8th of April 2020 (top row) as well as air quality (AQ) values for indicated pollutants (bottom row).
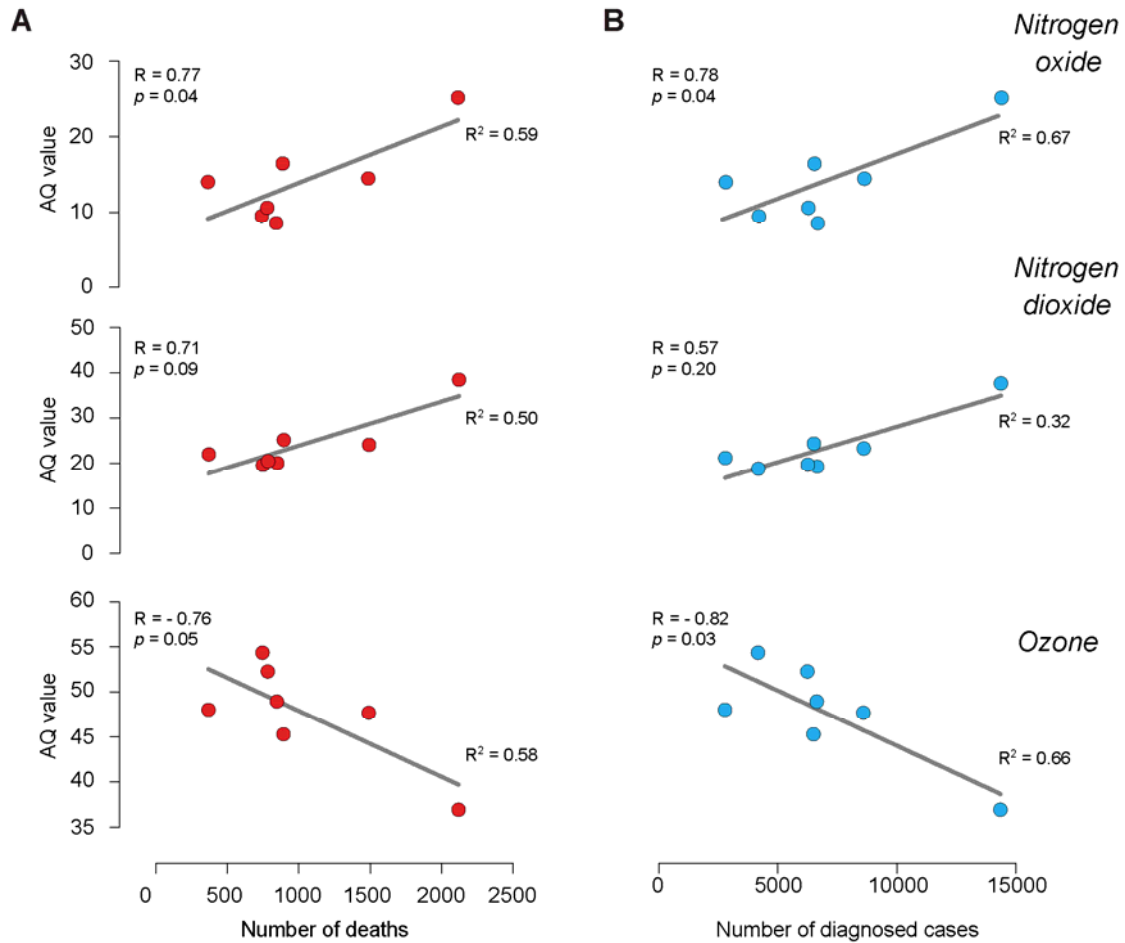
Figure 2. Correlation analysis of air pollutants and COVID-19.

Correlation between reported COVID-19 deaths (A, left column) and diagnosed cases (B, right column) vs air quality (AQ) values of indicated pollutants. R^2 is the linear correlation coefficient. The R and *p* values calculated from the two-tailed Pearson correlation test for data passing a normality test (nitrogen oxide and ozone) and Spearman correlation test for data that failed the normality test (nitrogen dioxide).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

MT, RP, YY and LMM planned and designed the study; MT, RP, YY collected the data; MT,

YY and NSJ treated and analysed the data; MT, RP, YY wrote the manuscript with support of

NSJ and LMM. MT, YY and RP conducted this work while in self-isolation due to the

current pandemic.

REFERENCES

1   Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).

2   Yi, Y., Lagniton, P. N. P., Ye, S., Li, E. & Xu, R. H. COVID-19: what has been learned and to be learned about the novel coronavirus disease. *Int J Biol Sci* **16**, 1753-1766, doi:10.7150/ijbs.45134 (2020).

3   Huang, C. *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497-506, doi:10.1016/S0140-6736(20)30183-5 (2020).

4   Wang, D. *et al.* Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*, doi:10.1001/jama.2020.1585 (2020).

5   Cao, X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*, 1-2, doi:10.1038/s41577-020-0308-3 (2020).

6   Wu, X., Nethery, R. C., Sabath, B. M., Braun, D. & Dominici, F. Exposure to air pollution and COVID-19 mortality in the United States. *medRxiv*, 2020.2004.2005.20054502, doi:10.1101/2020.04.05.20054502 (2020).

7   Guarnieri, M. & Balmes, J. R. Outdoor air pollution and asthma. *Lancet (London, England)* **383**, 1581-1592, doi:10.1016/S0140-6736(14)60617-6 (2014).

8   Wong, C. M. *et al.* Part 4. Interaction between air pollution and respiratory viruses: time-series study of daily mortality and hospital admissions in Hong Kong. *Research report (Health Effects Institute)*, 283-362 (2010).

9   Conticini, E., Frediani, B. & Caro, D. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? *Environmental Pollution*, 114465, doi:https://doi.org/10.1016/j.envpol.2020.114465 (2020).

10   Pannullo, F. *et al.* Quantifying the impact of current and future concentrations of air pollutants on respiratory disease risk in England. *Environmental health : a global access science source* **16**, 29, doi:10.1186/s12940-017-0237-1 (2017).

11   Gao, X. *et al.* Nitric Oxide Metabolites and Lung Cancer Incidence: A Matched Case-Control Study Nested in the ESTHER Cohort. *Oxidative medicine and cellular longevity* **2019**, 6470950, doi:10.1155/2019/6470950 (2019).

12   Cui, Y. *et al.* Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. *Environmental Health* **2**, 15, doi:10.1186/1476-069X-2-15 (2003).

13   Wang, L., Wang, J., Tan, X. & Fang, C. Analysis of NOx Pollution Characteristics in the Atmospheric Environment in Changchun City. *Atmosphere* **11**, 30 (2019).

14   Shan, J. *et al.* [The effect of short-term exposure to ambient NO(2) on lung function and fractional exhaled nitric oxide in 33 chronic obstructive pulmonary disease patients]. *Zhonghua Yu Fang Yi Xue Za Zhi* **51**, 527-532, doi:10.3760/cma.j.issn.0253-9624.2017.06.014 (2017).

15   Pathmanathan, S. *et al.* Repeated daily exposure to 2 ppm nitrogen dioxide upregulates the expression of IL-5, IL-10, IL-13, and ICAM-1 in the bronchial epithelium of healthy human airways. *Occup Environ Med* **60**, 892-896, doi:10.1136/oem.60.11.892 (2003).

16   Ji, X., Han, M., Yun, Y., Li, G. & Sang, N. Acute nitrogen dioxide (NO2) exposure enhances airway inflammation via modulating Th1/Th2 differentiation and activating JAK-STAT pathway. *Chemosphere* **120**, 722-728, doi:10.1016/j.chemosphere.2014.10.039 (2015).

17   De Weerdt, A. *et al.* Pre-admission air pollution exposure prolongs the duration of ventilation in intensive care patients. *Intensive care medicine*, doi:10.1007/s00134-020-05999-3 (2020).

18   Faustini, A., Rapp, R. & Forastiere, F. Nitrogen dioxide and mortality: review and meta-analysis of long-term studies. *The European respiratory journal* **44**, 744-753, doi:10.1183/09031936.00114713 (2014).

19   Bhatt, J. M. & Everard, M. L. Do environmental pollutants influence the onset of respiratory syncytial virus epidemics or disease severity? *Paediatric Respiratory Reviews* **5**, 333-338, doi:https://doi.org/10.1016/j.prrv.2004.07.003 (2004).

20   Weinberger, B., Laskin, D. L., Heck, D. E. & Laskin, J. D. The toxicology of inhaled nitric oxide. *Toxicological sciences : an official journal of the Society of Toxicology* **59**, 5-16, doi:10.1093/toxsci/59.1.5 (2001).

21   Zhang, J. J., Wei, Y. & Fang, Z. Ozone Pollution: A Major Health Hazard Worldwide. *Frontiers in immunology* **10**, 2518, doi:10.3389/fimmu.2019.02518 (2019).

22   Nuvolone, D., Petri, D. & Voller, F. The effects of ozone on human health. *Environmental science and pollution research international* **25**, 8074-8088, doi:10.1007/s11356-017-9239-3 (2018).

23   Hagenbjork, A., Malmqvist, E., Mattisson, K., Sommar, N. J. & Modig, L. The spatial variation of O3, NO, NO2 and NO x and the relation between them in two Swedish cities. *Environmental monitoring and assessment* **189**, 161, doi:10.1007/s10661-017-5872-z (2017).

24   Clausen, P. A., Wilkins, C. K., Wolkoff, P. & Nielsen, G. D. Chemical and biological evaluation of a reaction mixture of R-(+)-limonene/ozone: formation of strong airway irritants. *Environment international* **26**, 511-522, doi:10.1016/s0160-4120(01)00035-6 (2001).