Air pollutants and SARS-CoV-2 in 33 European countries

Rosalba Lembo¹, Giovanni Landoni¹², Lorenzo Cianfanelli¹, Antonio Frontera¹
¹IRCCS San Raffaele Scientific Institute, via Olgettina 60, Milan, Italy
²Vita-Salute San Raffaele University, Milan, Italy

Abstract. Background and aim: A potential correlation between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and air pollution has been suggested in some nationwide studies. It is not clear whether air pollution contributes to the spread of SARS-CoV-2 and related coronavirus disease 2019 (COVID-19) and to increase mortality. Methods: Data on COVID-19 incidence, mortality rate, air pollution, and greenhouse gas element of 33 European countries were extracted from public available databases and analysed with Pearson correlation analysis for the overall population and normalizing for the population over 65 years. Results: Air pollutant agents such as particulate matter <10µm (PM10), particulate matter <2.5µm (PM2.5), ammonia (NH3), sulphur dioxide (SO2), non-methane volatile organic compounds (NMVOCs), nitrogen dioxide (NO2) and greenhouse gas elements recorded showed a remarkable correlation with cumulative positive number of SARS-CoV-2 cases and with cumulative number of COVID-19 deaths. PM2.5 (r = 0.68, p-value = 0.0001 for cumulative positive cases; r = 0.73, p-value <0.0001 for cumulative deaths) and nitrogen oxides (r = 0.85, p-value <0.0001 for cumulative positive cases; r = 0.70, p-value 0.0001 for cumulative deaths) were among the pollutant agents with the strongest correlation for both positive cases and deaths. Conclusions: High levels of pollution in European countries should be considered a potential risk for severe COVID-19 and SARS-CoV-2-related death. (www.actabiomedica.it)

Key words: Air pollution; Atmosphere pollution; greenhouse gas emissions; ARDS; SARS-CoV-2; COVID-19

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is characterized in its severe forms by severe acute respiratory distress syndrome. The first outbreak was identified in Wuhan, China in December 2019. On March 11th 2020 World Health Organization (WHO) recognized the pandemic (1) when coronavirus disease 2019 (COVID-19) affected almost 120,000 people and spread over 110 countries (2).

One of most unknown characteristics of this pandemic is why some countries (e.g. Iran, Italy, Belgium, the Netherlands, United Kingdom and the United States of America) were among the hardest hit when compared to others. Several factors have been called into question as climate (3), population density (4), genetic of population (5) and spike protein mutation (6) which may cause an aggressive variant of the SARS-CoV-2 virus.

Air pollution has been correlated with SARS-CoV-2 outbreaks (7–9); and the persistence and the high contagion rate of some areas might be justified by certain orographic characteristics which, mixed with weather condition of poor rain fall, and absence of wind, may create a hood of air pollutants (10). Air pollution may favor the spread of the infection, increasing the number of contagion and the mortality rate. A possible explanation relies on the over expression of angiotensin-converting enzyme 2 (ACE-2) receptors at alveolar level in patients
chronically exposed to air pollutants (11). ACE-2 are known to be SARS-CoV-2 entry site in the cells (12), and increased expression may cause increased patient susceptibility. Furthermore, nitrogen dioxide (NO2), whose concentration in polluted areas is exceedingly high, has been called as potential booster for the higher mortality encountered in certain areas of the world (11). However, previous publications focused on Italy and data concerning other European countries are scarce. The aim of this research was to correlate SARS-CoV-2 outbreaks with air pollution in the entire Europe.

**Methods And Materials**

Number of SARS-CoV-2 positive and COVID-19 deaths per country were manually exported from the World Health Organization web site for the Situation Report number 118 (13).

Data of six air pollution agents (particulate matter < 10 µm - PM10, particulate matter < 2.5 µm - PM2.5, ammonia - NH3, sulphur dioxide - SO2, non-methane volatile organic compounds - NMVOCs and nitrogen dioxide - NO2) were extracted from the EUROSTAT website (14) with the last available data corresponding to 2017 and selected as “Total sectors of emissions for the national territory”. Another extraction was performed for Greenhouse gas emissions, listed as single elements from EUROSTAT based on European Environment Agency (EEA) information (15): Carbon dioxide; Methane; Nitrous oxide; Hydrofluorocarbons; Perfluorocarbons; Sulphur hexafluoride; were collected. Data were selected from labeling as “All sectors and indirect carbon dioxide (CO2) (excluding LULUCF and memo items, including international aviation)”. Last year of available data was 2017.

The rate of elderly (>65 years old) people in each European country except Liechtenstein was obtained from EUROSTAT and United Nations (16).

The European Countries included in the analysis are (in alphabetic order): Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Liechtenstein, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom. Twenty countries listed in WHO as European regions were excluded from analysis for missing data on EUROSTAT website: Albania, Andorra, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Georgia, Holy See, Israel, Kazakhstan, Kyrgyzstan, Monaco, Montenegro, North Macedonia, Republic of Moldova, Russian Federation, San Marino, Serbia, Ukraine and Uzbekistan.

**Statistical Analysis.** In order to investigate the potential relationship between air pollution agents, greenhouse gas emissions, SARS-CoV-2 positive cases and COVID-19 deaths in all analysed countries, Pearson correlation analysis was applied for the overall population, normalizing for the population over 65 years. Normalization for age was calculated as total number of cases (SARS-CoV-2 positive cases or COVID-19 deaths, respectively) divided by population aged >65 years multiplied by 1000. To control type I error rate due to multiple comparisons, Bonferroni correction was used and the adjusted level of significance was p < 0.05 after this correction. All statistical analyses were performed using the STATA 16 software with a threshold of significance, p = 0.05.

**Results**

A total of 1,480,130 SARS-CoV-2 positive cases were collected from 33 European countries from 11th February to 17th May 2020, in a time span of almost 14 weeks. Table 1 shows European countries demographic characteristics, number of SARS-CoV-2 positive cases and number of COVID-19 deaths.

The highest number of positive cases was collected from United Kingdom (n = 240,165), followed by Spain (n = 230,698) and by Italy (n = 224,760) as shown in Table 1. However, if we consider cases normalized for population aged over 65 years old we had Luxemburg (0.62), Iceland (0.50) and Spain (0.49) as the most hit countries in terms of SARS-CoV-2 positive cases.

Mortality was extremely variable among countries (Table 1). On 17th May 2020 the highest number of deaths was reached by United Kingdom (n = 34,466), followed by Italy (n = 31,763) and France (n = 27,578). However, after normalization according to population over 65 years old, the countries burdened by the highest number of deaths were Belgium (0.20) followed by Spain (0.15) and United Kingdom (0.14).
Table 1. Number of SARS-CoV-2 positive cases, number of COVID-19 deaths to SARS-CoV-2 infection, and demographic characteristics of 33 European Countries.

| Country          | Cumulative cases | Cumulative deaths | Population 2020 | Population over 65 | Normalized cumulative cases for population over 65 x 1000 | Normalized cumulative deaths for population over 65 x 1000 |
|------------------|------------------|-------------------|-----------------|-------------------|----------------------------------------------------------|----------------------------------------------------------|
| Liechtenstein    | 83               | 1                 | 38019           | —                 | 0.218312                                                 | —                                                        |
| Malta            | 546              | 6                 | 497724          | 184862            | 0.109699                                                 | 0.003246                                                 |
| Cyprus           | 914              | 17                | 885907          | 282148            | 0.103171                                                 | 0.006025                                                 |
| Luxemburg        | 3930             | 104               | 625669          | 177043            | 0.628128                                                 | 0.058743                                                 |
| Iceland          | 1802             | 10                | 358568          | 101378            | 0.502555                                                 | 0.009864                                                 |
| Estonia          | 1770             | 63                | 1326601         | 524106            | 0.133424                                                 | 0.012021                                                 |
| Slovenia         | 1465             | 103               | 2083676         | 825641            | 0.070308                                                 | 0.012475                                                 |
| Latvia           | 997              | 19                | 1905482         | 778054            | 0.052323                                                 | 0.002442                                                 |
| Lithuania        | 1534             | 55                | 2759230         | 1104620           | 0.055595                                                 | 0.004979                                                 |
| Croatia          | 2224             | 95                | 4054406         | 1677011           | 0.054854                                                 | 0.005665                                                 |
| Switzerland      | 30489            | 1601              | 8607483         | 3159444           | 0.354215                                                 | 0.050674                                                 |
| Slovakia         | 1493             | 28                | 5455848         | 1745346           | 0.027365                                                 | 0.001604                                                 |
| Bulgaria         | 2211             | 108               | 6943254         | 2983134           | 0.031844                                                 | 0.00362                                                  |
| Ireland          | 24048            | 1533              | 4943466         | 1378240           | 0.48646                                                  | 0.111229                                                 |
| Denmark          | 10858            | 543               | 5839809         | 2269841           | 0.185931                                                 | 0.023922                                                 |
| Hungary          | 3509             | 451               | 9739030         | 3778432           | 0.03603                                                  | 0.011936                                                 |
| Sweden           | 29677            | 3674              | 10348444        | 4067422           | 0.286777                                                 | 0.090328                                                 |
| Finland          | 6286             | 297               | 5528576         | 2407589           | 0.1137                                                  | 0.012336                                                 |
| Austria          | 16140            | 628               | 8908676         | 3335343           | 0.181172                                                 | 0.018829                                                 |
| Portugal         | 28810            | 1203              | 10261867        | 4478286           | 0.280748                                                 | 0.026863                                                 |
| Norway           | 8197             | 232               | 5369143         | 1835668           | 0.152669                                                 | 0.012639                                                 |
| Czech Republic   | 8455             | 296               | 10674178        | 4171430           | 0.07921                                                  | 0.007096                                                 |
| Belgium          | 54989            | 9005              | 11487179        | 4334844           | 0.478699                                                 | 0.207735                                                 |
| Romania          | 16704            | 1081              | 19282488        | 7185749           | 0.086628                                                 | 0.015044                                                 |
| Greece           | 2819             | 162               | 10691204        | 4699906           | 0.026368                                                 | 0.003447                                                 |
| Netherlands      | 43870            | 5670              | 17342709        | 6623729           | 0.252959                                                 | 0.085601                                                 |
| Italy            | 224760           | 31763             | 60233172        | 27541264          | 0.37315                                                  | 0.115329                                                 |
| Spain            | 230698           | 27563             | 47054924        | 18190878          | 0.490274                                                 | 0.151521                                                 |
| Turkey           | 148067           | 4096              | 83429615        | 7280089           | 0.177475                                                 | 0.056263                                                 |
| Poland           | 18257           | 915               | 37968244        | 13402471          | 0.048085                                                 | 0.006827                                                 |
| France           | 140008           | 27578             | 67204763        | 26813142          | 0.208331                                                 | 0.102853                                                 |
| United Kingdom   | 240165           | 34466             | 67086777        | 24500348          | 0.357992                                                 | 0.140676                                                 |
| Germany          | 174355           | 7914              | 83159604        | 35797688          | 0.209663                                                 | 0.022108                                                 |
Further details are given in Tables 2 which shows environmental levels of air pollutants and in Table 3 which shows greenhouse gas emissions across different European countries.

Air pollutant agents recorded across European countries in 2017 were put in correlation with both SARS-CoV-2 cumulative positive number of cases and cumulative number of COVID-19 deaths in Table 4.

| Country   | Ammonia | Nitrogen oxides | Non-methane volatile organic compounds | Particulates <10µm | Particulates <2.5µm | Sulphur oxides |
|-----------|---------|----------------|----------------------------------------|--------------------|---------------------|---------------|
| Liechtenstein | 213     | 492            | 241                                    | 39                 | 34                  | 16            |
| Malta     | 1113    | 5343           | 2815                                   | 378                | 238                 | 151           |
| Cyprus    | 6488    | 14543          | 12321                                  | 2054               | 1290                | 16391         |
| Luxemburg | 5805    | 18314          | 12101                                  | 2005               | 1345                | 1011          |
| Iceland  | 5280    | 22555          | 5628                                   | 1682               | 1284                | 49735         |
| Estonia  | 10255   | 33200          | 22245                                  | 13911              | 9222                | 38653         |
| Slovenia  | 18634   | 34711          | 29808                                  | 12986              | 11480               | 4878          |
| Latvia    | 16519   | 37421          | 38100                                  | 25009              | 17973               | 3996          |
| Lithuania | 29547   | 53437          | 45727                                  | 14196              | 9081                | 13177         |
| Croatia  | 37642   | 54852          | 63241                                  | 25378              | 16726               | 12557         |
| Switzerland | 55155  | 61149          | 78369                                  | 14922              | 6547                | 5424          |
| Slovakia  | 26545   | 65665          | 89478                                  | 22587              | 18068               | 27037         |
| Bulgaria  | 49440   | 102813         | 77232                                  | 47030              | 31967               | 103071        |
| Ireland  | 118496  | 110307         | 113349                                 | 27281              | 11970               | 13221         |
| Denmark  | 76333   | 111954         | 102258                                 | 31058              | 20061               | 10254         |
| Hungary  | 87700   | 119283         | 141520                                 | 68866              | 47988               | 27722         |
| Sweden    | 53336   | 124025         | 146939                                 | 40302              | 20098               | 17566         |
| Finland  | 31083   | 129850         | 88323                                  | 29179              | 17800               | 35020         |
| Austria  | 69095   | 144712         | 120189                                 | 27942              | 15613               | 12809         |
| Portugal  | 57606   | 159009         | 167536                                 | 72805              | 51268               | 47520         |
| Norway    | 33420   | 162730         | 152534                                 | 36860              | 27907               | 14925         |
| Czechia  | 67003   | 163205         | 207340                                 | 51280              | 39940               | 109962        |
| Belgium  | 66749   | 176273         | 109104                                 | 33408              | 23088               | 37573         |
| Romania  | 164336  | 231717         | 240088                                 | 143200             | 111925              | 106932        |
| Greece   | 55209   | 249536         | 148098                                 | 56505              | 25814               | 105844        |
| Netherlands | 132119 | 251905         | 252074                                 | 26928              | 14004               | 26898         |
| Italy    | 384192  | 709070         | 935000                                 | 195690             | 164677              | 115171        |
| Spain    | 518192  | 738890         | 617768                                 | 172098             | 105098              | 220443        |
| Turkey   | 739704  | 784697         | 1098974                                | 764935             | 16761               | 2350019       |
| Poland  | 307522  | 803661         | 690737                                 | 246310             | 147281              | 582656        |
| France   | 606358  | 807225         | 61960                                  | 254230             | 164487              | 143782        |
| United Kingdom | 283147 | 893108 | 809420 | 170786 | 106814 | 172877 |
| Germany  | 673251  | 1187502        | 1068758                                | 205986             | 99056               | 315477        |

* 1 tonne (metric) = 1 megagram (Mg) = 106 g
### Table 3. Greenhouse gas emissions across different European countries. All units of measurement are thousand tonnes*

| Country     | Carbon dioxide | Hydrofluoro carbones | Methane | Nitrogen trifluoride | Nitrous oxide (CO₂ equivalent) | Nitrous oxide | Perfluoro carbones | Sulphur hexafluoride |
|-------------|----------------|----------------------|---------|----------------------|--------------------------------|----------------|-------------------|-----------------------|
| Liechtenstein | 155.99         | 10.69                | 0.72    | —                    | 0.03                           | 9.74           | 0.02              | 0.05                  |
| Malta       | 2036.24        | 310.93               | 7.5     | —                    | 0.16                           | 46.97          | 0                | 0.99                  |
| Cyprus      | 8536.82        | 249.56               | 34.57   | —                    | 1.01                           | 301.38         | .                | 0.17                  |
| Luxemburg   | 10925.92       | 71.64                | 23.75   | —                    | 1.12                           | 332.68         | .                | 9.41                  |
| Iceland     | 4761.21        | 204.91               | 23.25   | —                    | 0.98                           | 293.36         | 68.04             | 2.31                  |
| Estonia     | 18833.81       | 236.24               | 42.84   | —                    | 3.08                           | 917.22         | .                | 2.44                  |
| Slovenia    | 14333.1        | 357.48               | 84.07   | —                    | 2.36                           | 702.27         | 17.45             | 15.81                 |
| Latvia      | 7680.07        | 234.92               | 72.19   | —                    | 6.8                            | 2025.81        | .                | 10.32                 |
| Lithuania   | 13724.6        | 711.26               | 130.3   | 0.01                 | 10.19                          | 3036.69        | .                | 7.73                  |
| Croatia     | 19165.83       | 488.71               | 164.33  | .                    | 5.72                           | 1703.32        | .                | 6.39                  |
| Switzerland | 43568.89       | 1511.7               | 194.17  | 0.54                 | 8.18                           | 2437.27        | 30.76             | 196.55                 |
| Slovakia    | 36198.66       | 739.06               | 184.05  | .                    | 6.47                           | 1928.21        | 8.62              | 7.08                  |
| Bulgaria    | 48114          | 1817.89              | 271.39  | .                    | 17.96                          | 5351.35        | .                | 17.51                 |
| Ireland     | 41764.18       | 1143.3               | 561.39  | 1.26                 | 22.74                          | 6775.51        | 47.2              | 39.22                 |
| Denmark     | 37981.3        | 405.43               | 275.39  | .                    | 18.39                          | 5479.42        | 1.09              | 75.45                 |
| Hungary     | 50341.26       | 1801.17              | 301.55  | .                    | 15.75                          | 4692.68        | 1.06              | 113.8                 |
| Sweden      | 44803.23       | 1138.31              | 180.75  | .                    | 16.47                          | 4907.42        | 36.58             | 47.09                 |
| Finland     | 46855.43       | 1278.58              | 184.25  | .                    | 15.79                          | 4705.6         | 5.84              | 50.23                 |
| Austria     | 72225.23       | 1724.77              | 263.91  | 12.01                | 11.82                          | 3523.79        | 44.09             | 399.03                |
| Portugal    | 58683.66       | 3257.1               | 379.17  | .                    | 10.55                          | 3144.33        | 16.87             | 25.25                 |
| Norway      | 45371.18       | 1402.75              | 200.95  | .                    | 8.09                           | 2410.05        | 130.96            | 58.83                 |
| Czechia     | 107389.4       | 3640.8               | 540.44  | 2.75                 | 19.62                          | 5846.77        | 1.37              | 74.31                 |
| Belgium     | 102366.5       | 2805.39              | 318.95  | 0.63                 | 20.06                          | 5976.58        | 167.66            | 92.03                 |
| Romania     | 76003.92       | 2177.68              | 1149.05 | .                    | 26.32                          | 7843.88        | 5.56              | 54.19                 |
| Greece      | 78279.35       | 6179.32              | 396.62  | .                    | 14.7                           | 4379.65        | 125.79            | 5.01                  |
| Netherlands | 176945.7       | 1826.38              | 721.31  | .                    | 29.6                           | 8821.28        | 77.03             | 126.38                |
| Italy       | 360157.6       | 15294.12             | 1754.17 | 23.5                 | 60                             | 17879.24       | 1313.68           | 417.49                |
| Spain       | 291353.4       | 6309.32              | 1600.64 | .                    | 61.79                          | 18414.7        | 127.77            | 225.6                 |
| Turkey      | 436344.4       | 8048.73              | 2167.81 | .                    | 129.62                         | 38626.84       | 73.11             | 73.12                 |
| Poland      | 339052.7       | 6893.27              | 1976.53 | .                    | 69.95                          | 20844.98       | 11.92             | 82.43                 |
| France      | 363707.1       | 18711.33             | 2250.3  | 7.64                 | 141.39                         | 42133.27       | 707.68            | 460.21                |
| United King- | 419518.5       | 14085.33             | 2058.36 | 0.53                 | 65.3                           | 19460.12       | 371.47            | 525.41                |
| Germany     | 827082.5       | 11010.81             | 2209.96 | .                    | 127.31                         | 37939.49       | 90.12             | 3834.33               |

* 1 tonne (metric) = 1 megagram (Mg) = 10⁶ g.
### Table 4. Air pollutant agents recorded across European countries in correlation with both cumulative SARS-CoV-2 positive cases and cumulative COVID-19 deaths.

| Air pollution agents                                      | Cumulative SARS-CoV-2 positive cases | Cumulative COVID-19 deaths |
|-----------------------------------------------------------|--------------------------------------|---------------------------|
|                                                           | Pearson's correlation | P value | Pearson's correlation | P value |
| Ammonia, t                                                | 0.81                    | <0.0001 | 0.62                  | 0.0013  |
| Nitrogen Oxides, t                                         | 0.85                    | <0.0001 | 0.70                  | 0.0001  |
| Non-methane volatile organic compounds, t                 | 0.86                    | <0.0001 | 0.64                  | 0.0002  |
| Particulates <10 µm, t                                     | 0.58                    | 0.0035  | 0.35                  | 0.44    |
| Particulates <2,5 µm, t                                    | 0.68                    | 0.0001  | 0.73                  | <0.0001 |
| Sulphur Oxides, t                                          | 0.35                    | 0.42    | 0.07                  | 0.99    |
| Greenhouse gas emissions                                   |                        |         |                       |         |
| Carbon dioxide, §                                          | 0.81                    | <0.0001 | 0.60                  | <0.0001 |
| Hydrofluorocarbons, §                                      | 0.83                    | <0.0001 | 0.83                  | <0.0001 |
| Methane, §                                                 | 0.83                    | <0.0001 | 0.70                  | <0.0001 |
| Nitrogen trifluoride, §**                                  | 0.46                    | 0.99    | 0.44                  | 0.99    |
| Nitrogen oxide, §                                          | 0.75                    | <0.0001 | 0.59                  | 0.0026  |
| Perfluorocarbons, §                                        | 0.64                    | 0.0030  | 0.77                  | <0.0001 |
| Sulphur hexafluoride, §                                    | 0.46                    | 0.067   | 0.23                  | 0.99    |

* ** data available for 9 countries  
  * data available for 27 countries

A significant association was found to be present as high levels of ammonia, nitrogen oxides, non-methane volatile compounds, particulate matter <10 micrometers, and particulate matter <2.5 micrometers were linked to high number of positive cases of SARS-CoV-2 infection. Similarly, high environmental levels of ammonia, nitrogen oxides, non-methane volatile compounds and particulate matter <2.5 micrometers were also associated with high number of deaths for COVID-19.

PM$_{2.5}$ ($r = 0.68$ with p-value $= 0.0001$ for cumulative positive cases; $r = 0.73$ with p-value $< 0.0001$ for cumulative deaths) and nitrogen oxides ($r = 0.85$ with p-value $< 0.0001$ for cumulative positive cases; $r = 0.70$ with p-value $0.0001$ for cumulative deaths) were the pollutant agents with the strongest correlation for both SARS-CoV-2 positive cases and COVID-19 deaths (see Table 1). Specifically, Figure 1 shows the linear correlation between PM$_{2.5}$ levels and normalized cumulative deaths for population over 65 years old per 1000, across European countries visually describing how countries with the highest levels of PM$_{2.5}$ (such as Spain, United Kingdom, France and Italy) are the one with the highest number of victims, circles were sized for population number.

### Discussion

The main finding of this research study is that both particulates and greenhouse gases high levels are associated with SARS-CoV-2 and that PM$_{2.5}$ and nitrogen oxides are among the pollutant agents with the strongest correlation for both SARS-CoV-2 positive cases and COVID-19 deaths. Environmental factors, such as urban air pollution, may play an important role in increasing susceptibility to severe outcomes of COVID-19.

Air pollution is responsible for almost 7 million deaths per year in the world (17). Particularly, the air pollution in urban area is a true cocktail of PM represented by gases, semi-volatile liquids, and particles. Our data suggest a strong link between certain air pollutants and high mortality reached in some countries. During the 2003 outbreak of SARS in China studies
have found higher mortality rates in urban regions with severe air pollution compared to low pollution areas, although these results were not adjusted for important confounders, such as age, sex and comorbidities (18).

Exposure to air pollutants is known to have detrimental effects on patients’ health, being associated with higher incidence of respiratory diseases, cardiovascular diseases and number of deaths. Possible explanations linking pollution to increased susceptibility to lung infections are local inflammation, decrease muco-ciliary clearance and exacerbation of underlying asthma and chronic obstructive pulmonary disease (20-22). Moreover, areas with elevated concentration of pollutants are the ones with the highest population density where disease transmission is favoured (23). It is therefore likely that a combination of the aforementioned factors may favour the establishment of overt COVID-19 infection and may promote different illness severity in different patients, eventually leading to the higher rate of mortality recorded in most polluted areas.

Our group has recently published the “double hit” hypothesis where we suggested that chronic exposure to PM$_{2.5}$ may cause over expression of angiotensin-converting enzyme (ACE-2) receptors (11). This may explain why children are preserved from SARS-CoV-2 infection. Furthermore, the double hit hypothesis is based on the enhancement caused by NO$_2$. This gaseous pollutant may be responsible for the high mortality in some countries where levels are high. Although the number of studies on this issue are still scarce, most results indicate that chronic exposure to air pollutants may leads to more severe and lethal forms of this disease and complicates recovery of COVID-19 patients. (24)

We acknowledge that the latest available data about air pollution agents and greenhouse gases publicly available is dated 2017.

**Conclusions**

After normalizing mortality data for population over 65 years old, air pollutants were associated to high SARS-CoV-2 infection and COVID-19 deaths.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership,
equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report -51, 11 March 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1baf2c57_10. [Accessed 15th February 2021]

2. Worldometer. COVID-19 Coronavirus Pandemic. Available at: https://www.worldometers.info/coronavirus/. [Accessed 15th February 2021]

3. Sajadi MM, Habibzadeh P, Vintzileos A, Shokouhi S, Miralettes-Wilhelm F, Amoroso A. Temperature, Humidity, and Latitude Analysis to Estimate Potential Spread and Seasonality of Coronavirus Disease 2019 (COVID-19). JAMA Netw Open. 2020;3(6):e2011834.

4. Rocklov J, Sjödin H. High population densities catalyse the spread of COVID-19. J Travel Med. 2020;27(3):taaa038.

5. Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov. 2020;6:11.

6. Korber B, Fischer WM, Gnanakaran S, et al. Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2. bioRxiv, p. 2020.04.29.069054, Jan.

7. Martelletti L, Martelletti P. Air Pollution and the Novel Covid-19 Disease: A Putative Disease Risk Factor [published online ahead of print, 2020 Apr 15]. SN Compr Clin Med. 2020;1-5.

8. Dutheil F, Baker JS, Navel V. COVID-19 as a factor influencing air pollution?. Environ Pollut. 2020;263(Pt A):114466.

9. Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. Sci Total Environ. 2020;727:138704.

10. Frontera A, Martin C, Vlachos K, Sgubin G. Regional air pollution persistence links to COVID-19 infection zoning. J Infect. 2020 Aug;81(2):318-356

11. Frontera A, Cianfanelli L, Vlachos K, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: The "double-hit" hypothesis. J Infect. 2020 Aug;81(2):255-259.

12. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.

13. World Health Organization. Coronavirus disease 2019 (COVID-19). Situation Report -118, 11 March 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200517-covid-19-sitrep-118.pdf?sfvrsn=21c0dafa_10. [Accessed 15th February 2021]

14. Eurostat. Air pollutants by source sector (source: EEA) (env_air_emis). Available at: https://ec.europa.eu/eurostat/cache/metadata/en/env_air_emis_esms.htm. [Accessed 15th February 2021]

15. Eurostat. Greenhouse gas emissions by source sector (source: EEA). Available at: https://ec.europa.eu/eurostat/cache/metadata/en/env_air_emis_esms.htm. [Accessed 15th February 2021]

16. United Nations: Department of Economic and Social Affairs. Population Dynamics World Population Prospects 2019. Available at: https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf. [Accessed 15th February 2021]

17. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, Kovacic JC. Oxidative Stress and Cardiovascular Risk: Obesity, Diabetes, Smoking, and Pollution: Part 3 of a 3-Part Series. J Am Coll Cardiol. 2017;70(2):230-251

18. Cui Y, Zhang ZF, Froines J, et al. Air pollution and case fatality of SARS in the People's Republic of China: an eco-logic study. Environ Health. 2003;2(1):15.

19. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet. 2017;389:1907-18.

20. Kurt OK, Zhang J, Pinkerton KE. Pulmonary health effects of air pollution. Curr Opin Pulm Med. 2016;22(2):138-143.

21. Faustini A, Stafoggia M, Colais P, et al. EpiAir Collaborative Group. Air pollution and multiple acute respiratory outcomes. Eur Respir J. 2013;42(2):304-13.

22. Cienciewicki J, Jaspers I. Air pollution and respiratory viral infection. Inhal Toxicol. 2007;19(14):1135-46.

23. Rubin D, Huang J, Fisher BT, et al. Association of Social Distancing, Population Density, and Temperature With the Instantaneous Reproduction Number of SARS-CoV-2 in Counties Across the United States. JAMA Netw Open. 2020;3(7):e2016099.

24. Ali N, Islam F. The Effects of Air Pollution on COVID-19 Infection and Mortality – A Review on Recent Evidence. Front Public Health. 2020;8:580057.

Correspondence
Professor Giovanni Landoni, MD
Associate Professor of Anesthesiology
Vita-Salute San Raffaele University
Department of Anesthesia and Intensive Care
IRCCS San Raffaele Scientific Institute
Via Olgettina, 60 – 20132, Milan, Italy
Tel. +39 02 2643 6158
Fax. +39 02 2643 6152
Email: landoni.giovanni@hsr.it
Twitter: @giovannilandoni - @SRAnesthesiaICU