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A first review to explore the association of air pollution (PM and NO_2) on severe acute respiratory syndrome coronavirus (SARS-CoV-2).

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Abstract

A new coronavirus (SARS-CoV-2) have determined a pneumonia outbreak in China (Wuhan and Hubei) on December 2019. While pharmaceutical and non-pharmaceutical intervention strategies are strengthened worldwide, the scientific community has been studying the risk factors associated with SARS-Cov-2, to enrich epidemiological information. For a long time, before the industrialized era, air pollution has been a real and big health concern and it is today a very serious environmental risk for many diseases and anticipated deaths in the world. It has long been known that air pollutants increasing the invasiveness of pathogens for humans by acting as a carrier and making people more sensitive to pathogens through a negative influence on the immune system. Based on scientific evidences, the hypothesis that air pollution, resulting from a combination of factors such as meteorological data, level of industrialization as well as regional topography, can acts both as an infection carrier as a harmful factor of the health outcomes of COVID-19 disease has been raised recently. This hypothesis is turning in scientific evidence, thanks to the numerous studies that have been launched all over the world.

With this review, we want to provide a first unique view of all the first epidemiological studies relating the association between air pollution and SARS-CoV-2. The Authors, who first investigated this association, although with great effort and rapidity of analysis dictated by a global emergency, often used different research methods or not all include confounding factors whenever possible. In addition, to date incidence data are underestimated in all countries, and to a lesser extent also mortality data. For this reason, the cases included in the considered studies cannot be considered real. Although it determines important limitations for direct comparison of results, and more studies are needed to strengthen scientific evidences and support firm conclusions, major findings are consistent, highlighting the important contribution of $PM_{2.5}$ and NO_2 on the COVID-19 spread and with a less extent also PM_{10}.

Keywords: Air pollution; Particulate Matter; Nitrogen dioxide; COVID-19; Pandemic

1. Introduction

A new coronavirus (SARS-CoV-2) have determined a pneumonia outbreak in China (Wuhan and Hubei) on December 2019. The scientific community has come together to implement effective preventive measures with a view to containing SARS-CoV-2 global spreads. Nevertheless, on March 11th 2020 WHO's Director-General announced that COVID-19 can be characterized as a pandemic. While pharmaceutical and non-pharmaceutical intervention strategies are strengthened worldwide, the scientific community has been studying the risk factors associated with SARS-Cov-2, to enrich epidemiological information.

SARS-CoV-2 is the etiologic agent of COVID-19, it is mainly spread by close contact (about 6 feet) with respiratory droplets. Symptoms are similar to other viral upper respiratory illnesses (Chavez et al., 2020) such as fever, cough, dyspnoea, and fatigue (Huang et al., 2020). The three main forms are a minor disease with the involvement of the upper airways, non-severe pneumonia, and severe pneumonia complicated by acute respiratory distress syndrome (ARDS) (Chavez et al., 2020; Chen et al., 2020). In experimental condition, it has be proven a convincing aerosol transmission of SARS-CoV-2 with the COVID 19 pathogen viable and infectious in aerosols for some hours and on surfaces up to days (van Doremalen et al., 2020), similarly with findings related to SARS-CoV-1 that is transmitted in association with nosocomial and super-diffusion events (Chen et al., 2004).

Acute respiratory distress syndrome (ARDS) is a form of non-cardiogenic pulmonary oedema, originated by injury to alveoli following an inflammatory pathway, that can beginning by lung or how systemic form (Sweeney and McAuley, 2016). In the twenty-first century we have had two new coronaviruses in humans: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), that are able to lead ARDS with high mortality (Martelletti and Martelletti, 2020).

Currently, it is unclear whether certain demographics of the population are more susceptible to infection with the novel coronavirus. Based on recent data, male gender, advancing age and co morbidities seem to be associated with death and severe illness (Harris et al., 2020). Furthermore, COVID-19 seems to be associated to an increasing rate of thromboembolic complications in hospitalized patients (Llitjos et al., 2020).

For a long time, before the industrialized era, air pollution has been a real and big health concern and it is today a very serious environmental risk for many diseases and anticipated deaths in the world. (GBD 2017 Risk Factor Collaborators, 2018). It has long been known that air pollutants increasing the invasiveness of pathogens for humans by acting as a carrier and making people more sensitive to pathogens through a negative influence on the immune system. (Becker and Soukup, 1999; Cai et al., 2007). One of the mechanisms by which ambient PM exerts its proinflammatory effects is the generation of oxidative stress by its chemical compounds and metals (Li et al., 2008; Signorelli et al., 2019). Due to the recovery in the PM, rising by numerous combustion sources, of environmentally persistent free radicals (EPFRs) we can assume a role of increasing in the severity of disease in the lower respiratory tract infections (LRTI) (Jaligama et al., 2017). Many studies reported an association between short- and long-term exposures to ambient air pollutants and numerous adverse health effects (e.g. higher mortality rates, greater hospital admissions, increased outpatient visits) (Bremner et al., 1999; Cohen et al., 2017; Dockery et al., 1993). It has notably deleterious effects on asthma, bronchitis, pneumonia and COPD (Dick et al., 2014; Perng and Chen, 2017; Raji et al., 2020; Vignal et al., 2017; Yarahmadi et al., 2018), where exacerbations and alterations in airway stability are often caused by bacterial and viral infections. Furthermore, air pollution is a recognized aggravating factor for infection diseases caused by viral infection such as respiratory syncytial virus (RSV), influenza A and B, para influenza virus type 3, pneumonia and influenza-like illness (Carugno et al., 2018; Croft et al., 2020; Fukuda et al., 2011; Huang et al., 2016; Huh et al., 2020; Liang et al., 2014; Lin et al., 2005; Silva et al., 2014; Somayaji et al., 2020), determining an increase in the rate of hospitalizations and access to emergency department visits. Evidences of such association was also reported with the spread of the SARS-CoV coronavirus, identified in November 2002 from the Guangdong province of southern China, causing an epidemic affected 26 countries and resulted in more than 8000 cases in 2003 and 774 deaths (Cai et al., 2007; Cui et al., 2003; Kan et al., 2005).

Based on scientific evidences, the hypothesis that air pollution, resulting from a combination of factors such as meteorological data, level of industrialization as well as regional topography, can become vector of the infection and harmful factor of the health outcomes of COVID-19 disease has been raised recently (Conticini et al., 2020; Frontera et al., 2020; Isaifan, 2020; Martelletti and Martelletti, 2020). This hypothesis is turning in scientific evidence, on the basis of the numerous studies that have been launched all over the world.

With this review, we want to provide a first unique view of all the first epidemiological studies relating the association between pollution and meteorological data with SARS-CoV-2, being aware that not all Authors had the time to study the interferences of confounding factors for obtaining a rigorous interpretation, and also, that associations were performed with very different methodologies of study.

2. Method

We selected representative original epidemiological studies on the association between severe acute respiratory syndrome SARS-CoV-2 and air pollution ($PM_{2.5}$, PM_{10} and NO_2) available online by April 26th, 2020. The research of epidemiological studies was conducted in PubMed, Scopus and Google Scholar databases. This review includes articles published in their final version, but also pre-proof and not reviewed preprints. We collected a total of N. 3 papers in their final version, N.1 paper in the pre-proof form, and N.9 papers in their preprint version.

3. Results

3.1 Particulate Matter

Particulate matter (PM) is an environmental pollutant coming into the atmosphere by very different wide antropic activities (Kim, 2013). It formed by a miscellaneous of solid and liquid particles suspended in air in a continue variation in size and composition (e.g. nitrates, sulphates, elemental and organic carbon, inorganic elements and organic and biological compounds (WHO, 2003).

PM has been associated with increased respiratory morbidity and mortality, especially in susceptible people, due to cardiorespiratory events, us well us asthma, chronic obstructive pulmonary disease, and atherosclerosis (Li et al., 2008; Signorelli et al., 2019; Yarahmadi et al., 2018). In vitro and in vivo studies highlighted its role in the exacerbation of respiratory viral infections (Becker and Soukup, 1999). Recently, the research group of Setti et al. (2020b) gave first preliminary evidence that SARS-CoV-2 RNA can be absorbed on outdoor particulate matter giving a suggestion that, in presence of big concentrations of PM and atmospheric stability situations, SARS-CoV-2 could create clusters with outdoor PM and enhance the persistence of the virus in the atmosphere.

First observations report a positive association between ambient concentrations of $PM_{2.5}$ (Guan et al., 2020; Pansini and Fornacca, 2020; Wang et al., 2020; Wu et al., 2020; Yao et al., 2020b; Zhu et al., 2020) and PM_{10} (Coccia, 2020; Guan et al., 2020; Pansini and Fornacca, 2020; Setti et al., 2020a; Yao et al., 2020b; Zhu et al., 2020) with COVID-19 pandemic across the most affected countries: China, Italy and U.S.A. Only one research group provides different conclusions (Ma et al., 2020).

In China Zhu et al. (2020) explored the relationship between particulate matter and the infection caused by the novel coronavirus in 120 cities in China. The Authors included over 58,000 (70%) of daily-confirmed new cases in the whole of China between January 23, 2020 and February 29, 2020. They applied a generalized additive model (GAM) to examine the effects of meteorological factors

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(the daily mean temperature (AT), relative humidity (RH), air pressure (AP) and wind speed (WS)) and air pollution, applying a moving-average approach to capture the cumulative lag effect of ambient air pollution. They observed a 10-μg/m^3 increase (lag0–14) in $PM_{2.5}$ and PM_{10} were respectively associated with a 2.24% (95% CI: 1.02 to 3.46) and 1.76% (95% CI: 0.89 to 2.63) rising in the daily numbers of COVID-19 confirmed cases. Similarly, Wang et al. (2020) applied a generalized additive model (GAM) as well, by controlling daily ambient temperature (AT), absolute humidity (AH) and population migration scale index (MSI), to verify the combnation between airborne PM pollution and daily numbers of confirmed case in 72 cities of China (excluded Wuhan city), observing more than 50 cases from January 20th to March 2nd, 2020. In cumulative lag effects, the pooled estimates of 72 cities were all significant and the strongest effects for both PM_{10} and $PM_{2.5}$ appeared in lag 014 and the RRs of each 10 μg/m^3 increase were 1.47(95% CIs:1.34, 1.61) and 1.64 (95% CIs:1.47, 1.82). In addition, they found that in all included lag days the effects of $PM_{2.5}$ on daily-confirmed cases were higher than PM_{10}.

Guan et al. (2020) with a time-series analysis conducted from Jan 25th to Feb 29th 2020 a retrospective cohort study taking into account COVID-19 incidence in Wuhan and XiaoGan, two worst hit cities in China. Results obtained from the Pearson regression coefficient analysis showed the incidence positively correlated with $PM_{2.5}$ in both cities (R^2=0.174 and $p<0.02$; R^2=0.23 and $p<0.01$, respectively), and with PM_{10} only in XiaoGan (R^2 =0.158 and $p<0.05$). Furthermore, they also found local temperature correlated with COVID-19 incidence in negative pattern, while no association was found with wind speed and relative humidity.

To determine the association between PM pollution level and the initial spread of COVID-19, an Italian study presented daily data relevant to ambient PM_{10} levels, urban conditions and virus incidence from all Italian Provinces from February 24th to March 13th. They highlighted that the Italian Northern Regions, the most affected by COVID-19, are also the regions with a high amount of PM_{10} and $PM_{2.5}$ going above the legislative standards (limit, 50 μg/m^3 per day) on February 2020 (Setti et al., 2020a). They highlighted how PM_{10} daily over limit value can be a significant predictor of infection.

Similarly, Coccia et al. (2020), by analyzed data on N=55 Italian province capitals, and data of infected individuals to April 7th, 2020, revealed an high association with rapid and wide diffusion of COVID-19 in Northern Italy and the air pollution measured in the days exceeding the set limits for PM_{10} in previous years. In particular, a very high average number of infected individual (about 3,600 infected individuals on 7th April, 2020) were observed in the cities having more than 100 days of air pollution (exceeding the limits set for PM_{10}) and a lower average number of infected (about 1,000 infected individuals) in the cities having less than 100 days of air pollution. The coastal cities have an average intensity of wind speed (about 12 km/h) higher respect the hinterland cities (8 km/h) and there was a negative coefficient correlation between infected subjects and wind speed intensity.

Other studies explore the association between COVID-19 case fatality and airborne PM. Pansini and Fornacca (2020), compared both COVID-19 cases and deaths, normalised by population size (100,000 residents) and airborne PM levels of Italy, USA and China. The collected diagnosed cases and deaths up to March 23 for Italy, March 24 for China and March 29 for U.S.A. They provide Pearson and Kendall correlation matrices and the corresponding coefficients, according to the distribution type, were analysed. Comparing $PM_{2.5}$ and PM_{10} data form ground measures retrieved from different databases (WHO for Italy, EPA for U.S.A and University of Harvard Dataverse for China) for previous years they found strong association with COVID-19 cases in all country only for $PM_{2.5}$ (China; tau =0.13 and $p<0.01$; Italy: tau=0.31 and $p<0.001$; U.S.A.: tau=0.08 and $p<0.02$), while only in U.S.A also for PM_{10} (tau=0.14 and $p<0.01$). Association with COVID mortality rate was performed only for China and U.S.A and they found a strong association for both PM fractions ($PM_{2.5}$: tau_{China}=0.19 and $p<0.001$; $tau_{U.S.A.}$=0.14 and $p<0.001$. PM_{10}: tau_{China}=0.11 and $p<0.01$; $tau_{U.S.A.}$=0.13 and $p<0.02$).

In China, Yao et al. (2020) studied both spatial and temporal association of particulate matter pollution and death rate of COVID-19. A cross-sectional analysis was performed to explore the spatial associations of death rate of COVID-19 concentrations in 49 cities including Wuhan, other 15 cities inside Hubei and 33 cities outside Hubei with the daily $PM_{2.5}$ and PM_{10}. They adjusted their results for temperature, relative humidity, gross domestic product (GDP) per capita and hospital beds per capita, trying a positive association between COVID-19 death rate and $PM_{2.5}$ (χ^2=13.10, p=0.011) and PM_{10} (χ^2=12.38, p=0.015). Furthermore, the authors conducted a time series analysis to look for the temporal associations day-by-day collecting both COVID-19 confirmed cases and deaths information, calculating the case fatality rate (CFR) with a 21-day lag considered from infection to death, examining also the lag effects and patterns of $PM_{2.5}$ and PM_{10} on CFR. They found how COVID-19 higher case fatality rate is related to increasing concentrations of $PM_{2.5}$ and PM_{10} in temporal scale especially with lag3 (r=0.65, $p=2.8\times10^{-5}$ and r=0.66, $p=1.9\times10^{-5}$, respectively). Contrary to Yao et al. (2020), findings of Ma et al. (2020) observed only a negative association of daily mortality with $PM_{2.5}$ and PM_{10}. The authors collected the daily death numbers occurred from January 20th to February 26th 2020 in Wuhan, China, and used a generalized additive model to examine if there is a link between the daily death counts of COVID-19 and the effect of pollutants, temperature, humidity and diurnal temperature range on, considered the lag effects on COVID-19 death of weather conditions. Furthermore, the study demonstrated a significant positive effect on the daily mortality of COVID-19 of the diurnal range of temperature, and a significant negative association between ambient temperature as well as relative humidity and COVID-19 mortality.

In the United States, Wu et al. (2020) investigated whether the risk of COVID-19 deaths increases, occurred up to April 04, 2020, is related to long-term average exposure to fine particulate matter ($PM_{2.5}$), by considering obout 3,000 USA counties (98% of the population). They also adjusted their results by population size, hospital beds, number of tested subjects, weather, and socioeconomic and behavioural variables. An increase of only 1 $\mu g/m^3$ in $PM_{2.5}$ have determined a 15% increase in the COVID-19 death rate (95% CI, 5%, 25%).

3.2 Nitrogen dioxide (NO2)

Nitrogen dioxide is a nasty-smelling gas formed by reaction in the atmosphere of nitrogen oxides (NOx) with other chemicals. NOx is naturally produced in atmosphere by lightning (Kang et al., 2019), volcanoes, oceans and biological decay (Thurston, 2017). The major outdoor anthropogenic sources of NOx are primarily emissions from transportation and fuel combustion, in particular, in urban areas they comes from vehicle exhaust gases and domestic heating (Grange et al., 2019; Maawa et al., 2020).

The nitrogen dioxide have mainly effect on the respiratory system. It is associated with several health effects such as elevated risks for asthma, allergic rhinitis and eczema in children (To et al., 2020), increase of outpatient visits and hospitalizations due to bronchitis and asthma exacerbation (Kowalska et al., 2020), increase of chronic obstructive pulmonary disease (COPD) (Pfeffer et al., 2019) and increase of pulmonary heart disease - related mortality (Chen et al., 2019).

A recent study explored the possible role of NO_2 in interference in Angiotensin converting enzyme 2 (ACE2) expression. The expression of ACE2 is high on lung alveolar epithelial cells and is the human cell receptor of virus agent of COVID-19 (Alifano et al., 2020). An increase in Angiotensin II binding to its receptor was observed In animal models with a 100-fold increase in ACE activity after exposure to NO_2 (Meulenbelt et al., 1992; Patel et al., 1990).

First observations report a positive association between ambient concentrations of NO_2 and COVID-19 pandemic across Europe, China and U.S.A (Guan et al., 2020; Ogen, 2020; Pansini and Fornacca, 2020; Travaglio et al., 2020; Yao et al., 2020a; Zhu et al., 2020). As well as for particulates matter, but the paper of Ma et al., (2020) provides different findings, reporting no association between NO_2 and mortality rate in in Wuhan, China.

Guan et al. (2020) and Zhu et al. (2020), by applying the same method explained for PM, observed that the COVID-19 incidence follows a positive pattern association with NO_2 in the city of Wuhan (R^2= 0.329 and p<0.001) and XiaoGa (R^2=0.158 and p<0.05), and that a 10-μg/m^3 increase (lag0–14) in NO_2 was associated with a 6.94% (95% CI: 2.38 to 11.51) increase in the daily numbers of COVID-19 confirmed cases in 120 cities of China, respectively. Pansini and Fornacca, (2020), by applying the same method explained for PM, compared also cases and deaths due to COVID-19 with tropospheric NO_2 quality information of Italy, USA and China, retrieved data from Sentinel-5 Precursor space-borne satellite. They found positive correlation between NO2 data and COVID-19 cases in China (tau = 0.12; p<0.01), U.S.A. (tau=0.20; p<0.001) and Italy (tau=0.52; p<0.001). Association with COVID mortality rate was performed only for China and U.S.A, as for PM, and they found a strong association both in China (tau = 0.10; p<0.02) and U.S.A (tau = 0.19; p<0.001). Travaglio et al., (2020) compared up-to-date, real-time SARS-CoV-2 cases and death measurements up to April 8 2020 from public databases across over 120 sites in different regions of England, with 2018 and 2019 annual average concentrations of NO_2 and NO. They applied the Pearson correlation coefficient, for normally distributed data (NO) or Spearman correlation coefficient for non-normally distributed data (NO_2). The Authors correlate high levels of two NOx with an increasing of mortality and spread in England by COVID-19. In particular, NO was found positive associated with both diagnosed cases and number of deaths (R^2= 0.67 and p<0.05, R^2= 0.59 and p<0.05, respectively), while the association with NO_2 was positive but not significant (R^2= 0.32 and p=0.20, R^2= 0.50 and p=0.09, respectively).

A cross-sectional study was performed by Yao et al.(2020a) to evaluate the spatial association of NO_2 levels with R_0 of COVID-19, as well, a longitudinal study to evaluate a day-by-day association between NO_2 and R_0 across 63 Chinese cities, collecting COVID-19 confirmed case information and hourly NO_2 data from the national databases. The cross-sectional study showed a positive association of R_0 with NO_2 in all cities ($\chi 2$=10.18 and p=0<0.05). The temporal association, conducted for the period between January 27 and February 26, was based on the daily R_0 of 11 cities in Hubei except Wuhan . They revealed that in all the 11 Hubei cities, but Xianning, there was a positive correlations between NO_2 (with 12-day time lag) and R_0 (r>0.51 and p<0.005), suggesting a time basis association between NO_2 and disease spread.

Ogen et al., (2020) in their study gave first results on the relationship between long-term exposure to NO_2 (including the months of January and February 2020 shortly before the COVID-19 spread in Europe) and novel coronavirus fatality in the most affected European countries, concluding that long-term exposure to NO_2 may be a potential contributor to mortality caused by SARS-CoV-2. He collected data concerning the fatality cases from 66 administrative regions in Italy, Spain, France and Germany and correlated mortality with NO_2 concentration in the troposphere measured by the Sentinel-5 Precursor space-borne satellite. The major tropospheric NO_2 hotspots identified was the Northern Italy. In all European regions considered, gas concentrations was between 177.1 and 293.7 μmol/m^2, with airflows directed downwards. Results show that out of the 4443 fatality cases by March 19, 2020, 3487 (78%) were in 5 regions of northern Italy and central Spain. Furthermore, by analysing mortality trends based on NO_2 concentrations it was revealed that the highest percentage of deaths were measured in geographical area where the maximum NO_2 concentration was higher than 100 μmol/m^2 (83%), with a significant decrease where the highest concentration was between 50 and 100 μmol/m^2 (15.5%), and below 50 μmol/m^2 (1.5%).

1. Conclusion

The first scientific evidences collected in the literature highlight the important contribution of air pollution on the COVID-19 spread. In particular, $PM_{2.5}$ and NO_2 were found to be more closely related to COVID-19 spread than PM_{10}.

The Authors who first investigated this association, although with great effort and rapidity of analysis dictated by a global emergency, used often different methods or not include all confounding factors whenever possible, such as control policy, urbanization rate, availability of medical resources, population size, number of cases, meteorological parameters, lifestyles and socioeconomic status.. In addition, to date incidence data are underestimated in all countries, and to a lesser extent mortality data. For this reason, the cases included in the considered studies cannot be considered real. Major findings of these studies are to be better evaluated because virus vitality and/or many confounding factors are not considered and it determines important limitations for direct comparison of results, and more studies are needed to strengthen scientific evidences and support firm conclusions.

For a long time we know how reducing outdoor and indoor air pollution in cities or countries can have a significant effect on health almost immediately, and the benefits can far outweigh the costs, according to a review of evidence from around the world. Surely, with the health emergency that the world is experiencing right now, we are learning that all the intellectual and economic resources are to be spent to accelerate actions to reduce the environmental burden including the air pollution decreasing.

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