A review of current knowledge on Pollution, Cigarette Smoking and covid-19 diffusion and their relationship with inflammation

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Summary. Coronavirus disease (COVID-19) is an infectious disease caused by the newly discovered coronavirus, Sars-Cov-2. This infection can cause mild to very severe respiratory and systemic illness mainly related with a cytokine storm. The epidemiology of COVID-19 is under continuous evolution, and studies are ongoing aiming at identifying the possible factors facilitating the diffusion of this infection. (www.actabiomedica.it)

Key words: Covid-19, pollution, smoking, inflammation

It is documented that air pollution and smoking are a leading cause of human morbidity and mortality globally, and can increase the risk of many diseases, including respiratory diseases. Overall, a linear relationship between exposure to atmospheric pollutants and diffusion of the Sars-Cov2 virus seems to exist. However, this correlation, cannot be regarded as a cause-effect relationship. The available data show that air pollution is responsible for inflammation and hyper-activation of innate immunity that are associated with the worst outcomes of covid-19 but do not allow to conclude that atmospheric particulate is responsible for increased contagion. As to smoking, nicotine activation of nicotinic receptors leads to enhanced protease activation, apoptosis and inflammatory signaling through the same pathways (Renin-angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2)) used by the virus increasing the inflammatory/destructive action of the virus itself.

The increase in non-communicable diseases and of chronic inflammatory diseases is in line with environmental pollution, related climate changes, and with an augmented susceptibility to infectious diseases with increased contagiousness and morbidity. Restrictive measures to limit environmental pollution are needed worldwide as this represents a threat for human health.

Introduction

Corona viruses represent a group of pathogens that co-infects humans and other vertebrates. These viruses damage the respiratory, gastrointestinal, and the central nervous systems, and the liver in humans, birds, bats, mice and many other wild animals. This class of viruses included two main types, zoonotic viruses, responsible for *Severe Acute Respiratory Syndrome* (SARS) and *Middle East Respiratory Syndrome* (MERS) in 2003 and 2004, respectively (1).

Since December 2019, a series of inexplicable cases of bilateral interstitial pneumonia were reported in the city of Wuhan, capital of the province of Hubei, in central China. In January 2020, the infectious agent considered to be the cause of these infections was identified by high throughput sequencing of the viral RNA genome. The *World Health Organization*

(WHO) called this new virus *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-COV-2), belonging to the ß-coronavirus cluster which include also the viruses responsible for SARS and MERS. The disease correlated with SARS-CoV-2has been defined as *Coronavirus disease* 2019 (COVID-19) (2).

The epidemiology of COVID-19 is under continuous evolution, therefore numerous studies are ongoing aiming at identifying the possible Fators facilitating the diffusion of this infection, among these pollution and smoking.

Atmospheric pollutants: atmospheric particulate

At present the polluting agents considered to be dangerous for human health and for the environment are: carbon monoxide (CO), lead (Pb), nitrogen dioxide (NO2), ozone (O3), sulfur oxide (SOx) and the atmospheric particulate (PM) (3).

PM is known to work as a *carrier, i*.e. as a transporting vector, for many chemical and biological contaminants, including viruses (4).

Viruses bind strongly to PM which is represented by both solid and/or liquid particles that can remain in the atmosphere for hours, days or weeks and that can diffuse and be transported even at long distances. Atmospheric particulate, besides being a *carrier*, represent also a **substrate** capable of leaving the virus in vital conditions in the air for a certain amount of time, hours or days. The rate of viral inactivation in the atmospheric particulate depends on the environmental conditions: whereas and increase in the temperatures and solar radiations have an accelerating effect on viral inactivation, a relatively high humidity can favour a higher rate of diffusion of a virus, thus its virulence(5).

Despite the fact that many studies have suggested an association bewteen exposure to atmospheric pollutants and increased risk of infection by respiratory viruses, the potential mechanisms behind this are largely unexplored and different scientific hypotheses have been put forward.

It has been hypothesised that polluting agents, as they can induce oxidative stress, might have a negative effect on the respiratory system through the production of free radicals (6),(7).

Some studies have shown instead that polluting agents might modulate the host's antiviral defenses reducing, among others, the ability of macrophages to phagocytate (8),(9).

It is well known that the surfactant proteins have an important role as part of the innate immune defense of the airways against viral pathogens. It has been shown that exposure to atmospheric pollutants can reduce the expression and change the function of hydrophilic surfactant proteins, as SP-A and D proteins, determining an increased susceptibility to infections caused by respiratory viruses (10).

Atmosheric pollution and respiratory infections

Several studies have shown a significant association between the degree of atmospheric pollution and the number of hospital admissions, due in particular to respiratory diseases. In consideration of the great impact of respiratory viral infections on morbidity and further on mortality, it is important to understand if and how the exposure to common atmospheric pollutants might aggravate susceptibility and severity of these infections (11).

With regard to these aspects, solid Literature that has addressed the associations, potential effects and mechanisms involved in the exacerbation of respiratory infections, is availabile. Among these studies, exposure to polluting agents emerges as an important factor.

In the first nineties, a study conducted by the Public health Department of the University of Helsinki, evaluated the effect of atmospheric pollution on the frequency of respiratory infections in infants and in preschool children, from Oulu, highly polluted, and in other two towns with scarce industrial atmospheric pollution.

As shown in Table 1, the children from both age-groups living in the most polluted town (highest PM levels) presented with a higher rate of respiratory infections, during the 12-month observation period, with respect to the children from the other two less polluted towns. The authors of this study, however, could not show whether the findings were due to PM only or to a synergic effect of PM, sulfur dioxide, hydrogen sulfide and other contaminants (12).

Table 1. Incidence of respiratory infections in the most and less polluted towns/areas in infants and preschool children.

	Polluted City						
N°of infections during the previous 12 months	More polluted area n(%)	Less polluted area (n%)	Total n(%)	Southern Reference City n(%)	Northern Reference City n(%)	Total n(%)	Unadjusted Odds Ratio (95% confidence interval)
		14 to 18	**months**	**old**	**children**		
0	15(8.0)	25(14.2)	40(11.0)	33(17.4)	32(25.6)	66(15.5)	1.0
1-4	134(71.3)	125(71.0)	258(71.1)	137(72.1)	74(59.2)	211(69.2)	1.9
≥5	39(20.7)	26(14.8)	65(17.9)	20(10.5)	19(15.2)	39(15.3)	2.7
Total	188	176	364	190	125	315	
		6	**year**	**old**	**children**		
0	29(21.8)	53(29.9)	82(26.5)	92(30.2)	67(46.5)	159(31.8)	1.0
1-4	97(72.9)	118(66.7)	215(69.3)	202(66.2)	76(52.8)	278(65.0)	1.5
≥5	7(5.3)	6(3-4)	13(4.2)	11(3.6)	1(0.7)	12(3.2)	2.1
Total	133	177	310	305	144	449	

A more recent chinese study described an association bwteen the diffusion of Respiratory syncytial virus (RSV) in children and the levels of PM. In detail, the (Average RSV positive rate %) was positively correlated with PM10 concentrations (fine particulate with an aerodynamic diameter below 10 μm) and of PM2.5 measured as $\mu g/m^3$ (13).

It is likely that exposure to PM 2.5 could contribute, at least in part, to increase:

- suscebtibility towards respioratory viruses;
- exposure to these pathogens;
- severity of the infection itself.

These are the conclusions that arose from an american study that evaluted the existing correlation between PM2.5 emission and low respiratory tract infections (in particular from RSV and influenza viruses), in a large series of children from Utah (146.397), stratified according to age (0-2, 3-17, 18>) (14).

A chinese study in 2020 from the Lanzhou region reported that one of the main causes of daily diffusion of measles was represented by the levels of pollution by PM. Moreover, interestingly, the daily cases of measles were increased in the days with mild temperatures, high wind velocity, low relative humidity and high air pressure (15).

Coronavirus and atmospheric pollution

SARS

The significant differences in the mortality rates for SARS in different geographic areas of China, led to the hypothesis that different levels of air pollution, could account at least in part for this phenomenon.

A 2003 chinese study analysed the data related wth morbidity and mortality for SARS in 5 different regions of China with a number of affected cases equal or above 100 and the levels of pollution in the same areas. Almospheric pollution was measured using the air pollution index (API) derived from the concentrations of particulate, sulfurdioxide, nitrogen dioxide and ozone at ground level.

This study showed that the patients coming from the regions with highest API had double the probability of dying of SARS with respect to those coming from areas with a low API. The analysis based on long-term exposure to atmospheric pollutants showed a similar association (16). (*Table 2*)

Similar results were reported analysing the levels of PM10, SO2 and NO2, between April 25th and May 31st 2003 in the city of Beijin and daily mortality for SARS. This latter was positively correlated with the

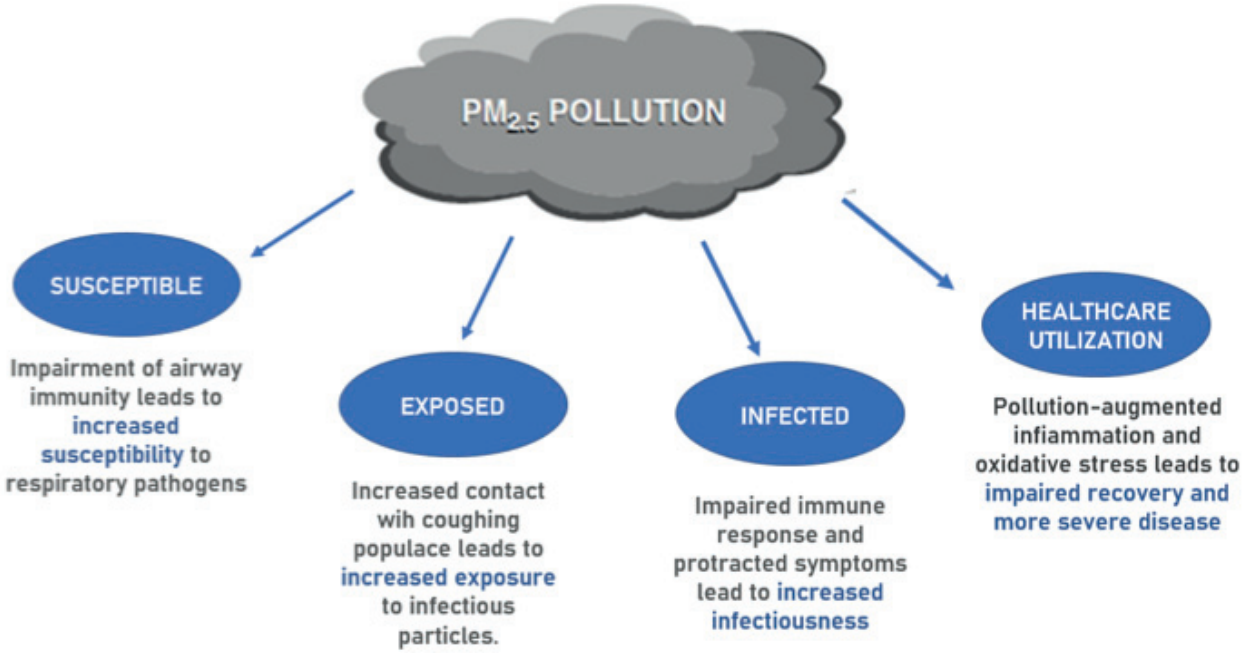

Figure 1. Possible mechanisms of action of PM 2.5 on infections by respiratory viruses

Table 2. Mortality rate for SARS in the regions based on a high (>100), intermediate (75-100) and low (< 75) API*.

API	Number of Deaths	Number of recovered	Total Number of Cases	Case Fatality	RR & 95% CI
>100	17	174	191	8.90%	2.18 (1.31-3.65)
75-100	269	3321	3590	7.49%	1.84(1.41-2.40)
<75	63	1483	1546	4.08	1
Total	349	4978	5327	6.53%	

*Air pollution Index

level of atmospheric pollutants analysed, confirming the findings above (17).

COVID-19

A study carried out by the Italian Society for environmental medicine (SIMA), with the Universities of Bari and Bologna, evidenced a correlation between the overruns of the limits for PM10, measured by the controllers of a number of towns, and the number of admissions for COVID-19 (18).

Further, for each Italian province the following were analysed:

- The data relative to the daily PM10 concentrations detected by the Regional Agencies for the protection of the environment (ARPA) from all over Italy, considering the number of overruns according to the limit established by law (50 μg m-3) relative to daily PM10 concentrations, adjusted for the number of active controllers for each province;

- the number of COVID-19 positive cases reported in the CIVIL PROTECTION website (COVID-19 ITALIA).

In particular, a linear relationship was clear between the overruns according to the limits established by law for PM10, registered between February 10th-February 29th, and the number of COVID-19 affected subjects updated on March 3rd (considering a mean intermediate lapse of approximately 14 days equivalent to the time of incubation of the virus and the identification of the infection).

Furthermore, studying the expansion curves of the infection in the different regions, it is clear that:

- The regions placed in the centre-south of Italy show a trend compatible with epidemiological models typical of a person-person transmission;
- The regions in the Padana Plane, where the outbreaks appear to be particularly virulent, show abnormal accelerations;

This latter datum would reasonably lead to the hypothesis of a diffusion mediated by a *carrier*. This would be confirmed, by the presence of phases of boosting concomitant with elevated PM10 concentrations, above the admitted limit.

However, this is a correlation based on a limited number of observations, and thus on an hypothesis that requires to be verified, which deserves to be confirmed and deepened by means of a more evoluted study design (18).

A recent study by the University of Siena has further investigated the relationship between the high mortality rate and atmospheric pollution in the North of Italy (in particular Lombardy, Veneto, and Emilia Romagna). According the the data of the Civil Portection updated to March 21st 2020, the mortality rate in Lombardy and Emilia Romagna regions was 12%, whereas approximately 4,5% in the rest of Italy (19).

The European Environment Agency (EEA) has recently introduced the *Air Quality Index* (AQI), that reflects the potential impact of the quality of air on health, which is influenced by the polluting agents in different geographic areas. The different key pollutants are measured every hour, by over two thousand monitoring stations of the quality of air all over Europe, among these: PM10, PM2.5, O3, SO2 and NO2. Based on these measurements, the AQI in Lombardy and in the Emilia Romagna regions are amongst the highest in Italy (20).

This study is based on important premises, scientifically proven by previous studies. Atmospheric pollution represents one of the most well known causes of log lasting inflammation, leading to an hyper-activation of the cells of innate immunity.

Interleukin 4 (**IL-4**), tumour necrosis factor alpha (TNF-α) and TGF beta (TGF-ß1) were found to be increased both in serum and lung cells besides in leukocytes and macrophages of mice after exposure for three months to PM 2.5 (21). These results have been confirmed in humans: both PM2.5 and PM10 determine systemic inflammation and increased Platelet Derived Growth Factor (PDGF), vasoendothelial growth factor (VEGF), TNFα, IL-1 and IL-6, and this is observed also in healthy subjects, non-smoking and young adults, and appears to have a direct relationship with the time of exposure to the pollutants (22),(23).

All these factors are elevated in patients with covid-19 and related with most of the findings and symptoms reported in the patients with the worst outcomes, specifically acute cardiac and kidney injury, shock, vasculitis, thrombosis, disseminated intravascular coagulation besides acute respiratory distress syndrome (24), (25). Most of these cytokines are increased in conditions such as obesity and diabetes mellitus, in particular type 2 diabetes when insulin resistance is clearly present (26),(27). Therefore, under thsese conditions a basal inflammatory condition already present and exacerbated by pollution, can easily contribute to explain further why subjects with obesity appear to be at increased risk of COVID-19 (28),(29).

Finally, pollution compromises the first line of defense of the upper airway tract, i.e. the cilia (30), therefore, a subject living in a high pollution area could be more prone to develop both infectious and chronic respiratory diseases.

One of the most fearsome events associated with SarsCov-2 is A*cute Respiratory Distress Syndrome* (ARDS), which treatment is usually only supportive and requires mechanical ventilation.

Independent of aetiology (31), a hyper-activation of the immune system is thought to have a fundamental role in this condition: cytokines and chemokines such as TNFα, IL 1b, IL-6, IL-8, IL-17 and IL-18 besides other growth factors are over-expressed in ARDS and become responsible for the activation of the activation of the apoptotic cascade (32).

In conclusion, based on this italian study, the chronic inflammatory stimulus and the dysregulation of the immune system induced by the prolonged exposure to pollluting agents, even in young and healthy subjects, could contribute to explain the increased lethality for COVID-19 observed in some geographical areas, such as in regions in the North of Italy (19).

America has also pointed its attention to the pollution problem and to its role during the COVID-19 pandemia. A very recent study from the University of Harvard has investigated the relationship between long term exposure to PM2.5 and Sars-Cov2 mortality rate in the United States. This study stands on solid background based on the well known effects of PM2.5 on the conditions of health of single individuals and on the evolution of respiratory, cardiovascular and neuro-cognitive diseases as well as on the *outcome* of pregnancy both in the United States and in the world, all well known and consolidated data (33),(34),(35),(36),(37).

Moreover, in 2017, the same group from the Department of biostatistics of the Univesity of Harvard, had analysed the causes of death in the United States population belonging to the *Medicare category* (insurance programme in the United States including subjects older than 65yr or responding to specific criteria) from 2000 to 2012 finding that short term exposure to PM 2.5 and ozone during the summer, was significantly associated with an increased mortality rate (38).

According to the findings of a recent study an increase of 1 μg / m^3 in PM 2.5 is associated with a 15% increase in the mortality rate for COVID-19, with a confidence interval of 95% (CI) (5%, 25%). This means that in a single county as New York (Manhattan) a long term reduction of only 1 μg/m3 in the mean exposure to PM 2.5 would have determined 248 less deaths on a total of 1905 deaths for COVID-19 registered up to April 4th 2020 (39).

PM is not the only polluting agent for which a relationship with COVID-19 infection has been hypothesised. Nitrogen dioxide (NO2) is a toxic gas produced principally by the combustion of fossil fuels. A prolonged exposure to NO2 has been associated with hypertension (40), cardiac and cardiovascular diseases (41), increase in hospitalization rate (42), chronic obstructive bronchopneumopathy (BPCO) (43), significant defects in the development of pulmonary function in children (44), reduced pulmonary function in adults and lung lesions (45) and diabetes (40).

A German study has examined the relationship between longterm exposure to NO2 and severity of infection by SarsCov2.

The data from the *Esa Sentinel 5P satellite* were analysed, mapping the distribution of NO2 in Europe in the months that preceeded the pandemy. At the same time the number of deaths caused by Coronvirus in 66 regions of Spain, Italy, France and Germany were traced up to the 19th of march. What emerged was that 3487 out of 4443 deaths, equivalent to 78% of cases, were concentrated in five areas located in North of Italy, and Central Spain, where high levels of NO2 combine with an air flow directed towards the earth that would prevent an effective dispersion of atmospheric pollution. This data suggest that longterm exposure to this pollutant could contribute importantly to the mortality rate for COVID-19 in these regions and probably worlwide (46).

Nicotine and COVID-19

Cigarette smoke has been for long recognised as an important cause of cardiovascular and lung diseases, through its direct action on nicotinic receptors highly expressed in cardiac tissue, in blood vessels and lung cells (47),(48).

It can damage the pulmonay system through different mechanisms as cytokine activation (inflammatory and activating apoptosis) and direct action the immune system cells (ex. T lymphocytes) (49).

A very recent american study has tried to identify the mechanism behind the interaction between nicotinic receptors and COVID-19 infection (50).

The spike (S) protein of coronaviruses facilitates viral entry into target cells. Entry depends on binding

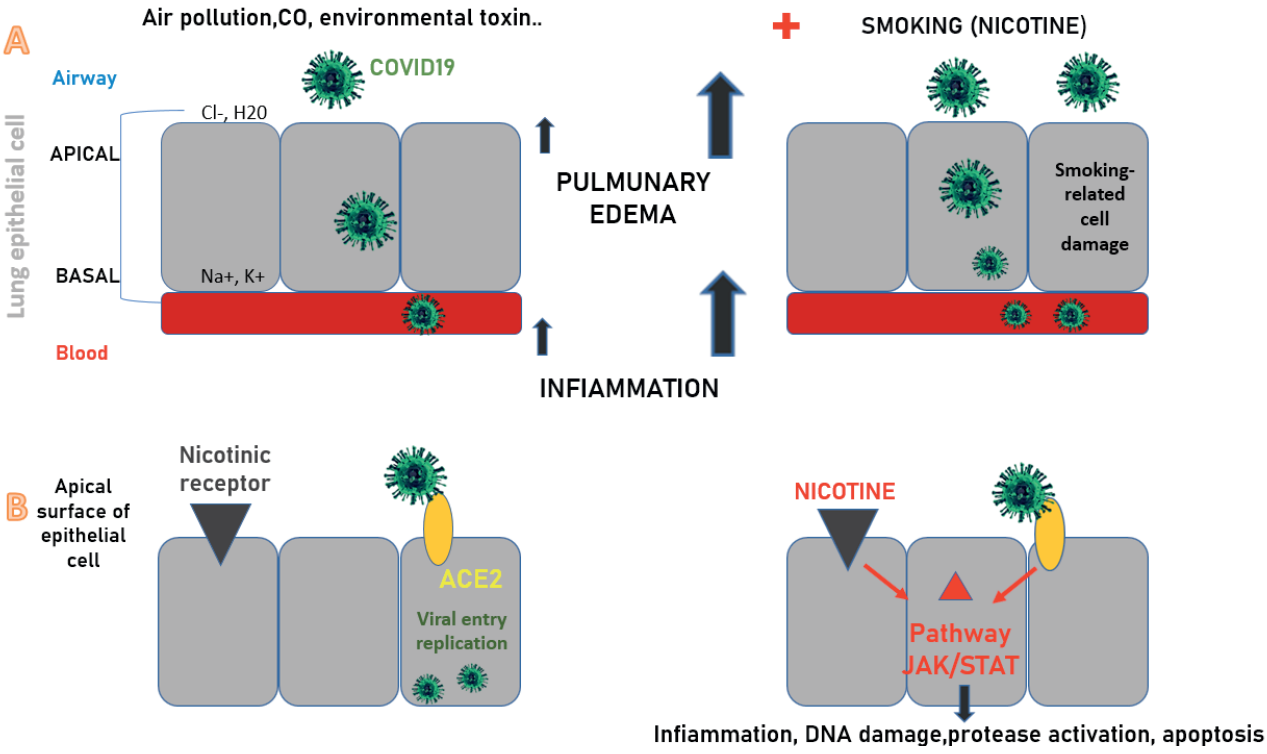

Figure 2. A. Changes in response to COVID 19 entrance into epithelial bronchial cells in smokers (right panel) and in non-smokers (left panel). **B.** co-expression of ACE2 and nicotinic receptors on the apex of cell. They both activate the JAK-STAT pathway increasing further the inflammatory/necrotic process.

of the surface unit, S1, of the S protein to a cellular receptor, which facilitates viral attachment to the surface of target cells. SARS-S engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor. Entry of CoVs into the host cells is mainly mediated by the endocytic pathway, clathrin-mediated, meanwhile autophagy has also been implicated in the viral replication in the cells (51).

ACE2 is abundantly present in humans in the epithelia of the lung and small intestine, and is also present in vascular endothelium providing some understanding of the pathogenesis of the infection (52).

In many cells in the lung (including bronchial epithelial cells, alveolar macrophages, endothelial cells and interstitial fibroblasts), nicotinic receptors are co-expressed with most of the components of the Renin Angiotensin System (RAS) (50).

Renin-angiotensin system (RAS) is an important endocrine system that regulates cardiovascular physiology and participates in pulmonary injury by activating inflammatory factors in the lung (53), (54). The angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/Ang II type I receptor (AT1R) (ACE/Ang II/AT1R) axis and angiotensin-converting enzyme II (ACE2)/angiotensin 1-7 (Ang-(1-7))/Mas receptor (ACE2/Ang-(1-7)/Mas) axis represent two pathways with opposing effects within this system (55) counter-regulating the expression of pro-inflammatory factors. Increased ACE levels cause the activation of AT1R by Ang II, inducing the expression of the pro-inflammatory cytokines IL-6, TNF-α and TGF-β1 (56). ACE2 counter-regulates the effects produced by Ang II by converting Ang II to Ang-(1-7), and activating the Mas receptor that in turn represses the signaling pathways via STAT3 and extracellular signal-regulated kinases (ERK) (57), working as an anti-inflammatory factor (58).

Nicotine activation of nicotinic receptors can lead to enhanced protease activation, cell death (apoptosis), and inflammatory signaling throught the same

pathways increasing the inflammatory/destructive action of the virus (50).

In addition to nicotine, cigarettes contain toxins such as carbon monoxide and polycyclic aromatic hydrocarbons, which also perturb the function of the cardiovascular, pulmonary, and immune systems, and at this point, such toxins may also contribute to COVID-19 disease outcome (50).

Considering the well documented importance of ACE2 receptors for the entrance of SarsCov2 into the host cell, ACE2 gene expression has been studied in different cells considering race, age, sex and smoking habits, in order to identify possible differences among patients that may determine a greater susceptibility to infection. A significant increase in ACE2 expression was found in the lungs of subjects who smoked: in detail, ACE2 appears to be actively expressed in the goblet cells of the bronchial epithelium and in type II pneumocytes of smoking patients. This suggests that smoking should be considered as a risk factor that increases susceptibility to COVID-19 (59).

Finally, a systematic review of the Literature revised 5 studies that included information relative to smoking habits, to evalute any association bewteen smoking and the outcome of COVID-19 infection including the severity of the disease, the need for mechanical ventilation, the need for admission in an intensive care unit (ICU) and death (60). The study with the largest series of patients suggested that smoke was probably associated with a negative progression and the worst outcomes of COVID-19 (61).

Conclusions

The changes in the climate of our Planet, for which mankind has had over years an increasing responsibility, forces us to focus on the multiple effects correlated with this, and on the increasingly necessary solutions to be implemented.

The greater susceptibility to infectious diseases along with their increased contagiousness and morbidity represent to date an important problematic which is potentially related with the above mentioned climate changes and with environmental pollution.

The increase in non-communicable disaeses such as diabetes, and overall of chronic inflammatory diseases is also in line with this latter observation**.**

Referring specifically to COVID-19, the studies which are continuously updated have highlighted a possible linear relationship between exposure to atmospheric pollutants and diffusion of the virus, putting the basis for understanding the aetiopathogenetic mechanisms of this infection. This correlation, however, should not be regarded as a cause-effect relationship and the data currently available do not allow to say that the atmospheric particulate is responsible for an increased contagion. Therefore, further studies addressing this issue are warranted.

What can be said instead with reasonable convincement, and seems to be confirmed by the Literature reported in this article, is that we need restrictive measures to limit environmental pollution as it represents a worlwide threat for human health.

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.

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