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Exposure to particulate matter: Direct and indirect role in the COVID-19 pandemic

Ana Santurtún [a,*], Marina L. Colom [a], Pablo Fdez-Arroyabe [b], Álvaro del Real [c], Ignacio Fernández-Olmo [d], María T. Zarrabeitia [a]

[a] Legal Medicine and Toxicology Area, Department of Physiology and Pharmacology. Faculty of Medicine. University of Cantabria, Santander, Spain
[b] Geography and Planning Department, Geobiomet Research Group. University of Cantabria, Santander, Spain
[c] Medicine and Psychiatry Department. University of Cantabria, Santander, Spain
[d] Chemical and Molecular Engineering Department. University of Cantabria, Santander, Spain

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ABSTRACT

Knowing the transmission factors and the natural environment that favor the spread of a viral infection is crucial to stop outbreaks and develop effective preventive strategies. This work aims to evaluate the role of Particulate Matter (PM) in the COVID-19 pandemic, focusing especially on that of PM as a vector for SARS-CoV-2.

Exposure to PM has been related to new cases and to the clinical severity of people infected by SARS-CoV-2, which can be explained by the oxidative stress and the inflammatory response generated by these particles when entering the respiratory system, as well as by the role of PM in the expression of ACE-2 in respiratory cells in human hosts.

In addition, different authors have detected SARS-CoV-2 RNA in PM sampled both in outdoor and indoor environments. The results of various studies lead to the hypothesis that the aerosols emitted by an infected person could be deposited in other suspended particles, sometimes of natural but especially of anthropogenic origin, that form the basal PM. However, the viability of the virus in PM has not yet been demonstrated. Should PM be confirmed as a vector of transmission, prevention strategies ought to be adapted, and PM sampling in outdoor environments could become an indicator of viral load in a specific area.

1. Introduction

Infectious diseases are considered the main causes of human morbidity and mortality. Humans have faced numerous epidemics throughout history. Although significant progress has been made in the prevention and treatment of several pathogens, the reappearance of viral agents remains a major threat and challenge for health systems (Michaud, 2009).

Different factors underlie the appearance of these diseases, such as the increase in population, the rise in global connectivity, the type of social interactions, the prevalence of immunosuppressive diseases, the change in agricultural practices and some other environmental factors (Mani et al., 2012). In relation to the latter, different authors have analyzed the impact of climate change and the reduction in biodiversity in epidemics.

It should be noted that 60% of infectious diseases and 70% of emerging infections are of zoonotic origin in humans (Michaud, 2009). The disturbance of natural ecosystems increases the transfer of diseases from wild species to humans and it could cause new infectious diseases and increase the incidence of neglected diseases (Epstein et al., 2003). Changes in climate can force species to change their geographical distribution towards semi-natural habitats, closer to humans (Lorentzen et al., 2020), or even cause the re-emergence of apparently extinct diseases, by allowing the appearance of pre-existing or new pathogens or transmission vectors of diseases (Zell, 2004).

Air pollution, in addition to being one of the factors responsible for climate change, and therefore indirectly one of the variables to be considered among those that cause the emergence of these diseases, also plays a role in the vulnerability of infection and in the clinical severity afterwards.

In this line, Hsiao et al. have recently described that fine particles found in the air are a direct transmission mechanism for influenza virus

* Corresponding author. Legal Medicine and Toxicology Area, Department of Physiology and Pharmacology. Faculty of Medicine. University of Cantabria, Av Cardenal Herrera Oria s/n, 39011, Santander, Spain.

E-mail address: ana.santurtun@unican.es (A. Santurtún).

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infection to the human alveolar epithelium, and that chemicals in PM2.5 may play vital roles in terms of viable influenza virus in the atmosphere (Hsiao et al., 2022).

In recent decades, several diseases caused by viral agents have emerged (such as SARS-CoV [SARS-CoV-1], MERS-CoV, H5N1, H1N1 and H7N9, among others) (Wei et al., 2016). Society is currently facing the COVID-19 pandemic, derived from the disease caused by the SARS-CoV-2 virus, and the study of its risk factors has gained great interest, both for its incidence and for the severity of morbidity and associated mortality.

The study of the role of air pollution and specifically of small-diameter particulate matter (PM) in COVID-19 has led to the development of numerous research projects over the last year, with both epidemiological and experimental approaches. On the one hand, since the effects of small diameter PM at the respiratory and immunological system are known, some authors hypothesized that exposure to this pollutant could enhance the clinical manifestations of infected people (Marquès and Domingo, 2021; Conticini et al., 2020; Domingo and Rovira, 2020) or affect the susceptibility of the individual to the infection (Murgia et al., 2021; Woodby et al., 2021; Bontempi et al., 2020).

On the other hand, it has been suggested that the aerosols generated by an infected person can be deposited on solid PM suspended basally in outdoor and indoor environments, thus acting as a transmission vector (Setti et al., 2020; Nor et al., 2021).

Finally, other experimental studies have analyzed the relationship between the expression of certain enzymes and PM pollution. In particular, the expression of Angiotensin-converting-enzyme-2 (ACE-2), an enzyme via which SARS-CoV-2 enters human target cells and that has been identified as a receptor for this virus, has been linked to the exposition to PM (Wan et al., 2020).

In this context, this review has 3 objectives: i) To assess the relationship between PM contamination, the clinical severity of cases, and associated mortality; ii) To analyze the role of PM as a vector for SARS-CoV-2; and iii) To evaluate the relationship between ACE-2, PM and COVID-19, Fig. 1.

2. Particulate matter

Particulate matter is the sum of chemical and biogenic compounds, of natural and/or anthropogenic origin, whose size varies between 1 nm and 100 μm, and which are found in the air and can be diffused and transported even over long distances. PM less than 10 μm is deposited at different levels of the respiratory tract, depending on its size: coarse particles, with an aerodynamic diameter ranging from 2.5 to 10 μm (PM10–2.5), can initially be deposited in the upper respiratory tract and may be later swallowed, while fine particles (PM2.5) can accumulate in the lung parenchyma, inducing various respiratory diseases (Falcon-Rodriguez et al., 2016).

However, PM presents large variability not only in size, but also in chemical composition. PM can be made up of organic, inorganic, and biological compounds. The geographical characteristics (both climatic and orographic), anthropogenic sources and atmospheric conditions at a given moment are determining factors in its structure and toxicity.

Finally, in relation to PM transport, the dispersion of the particles can

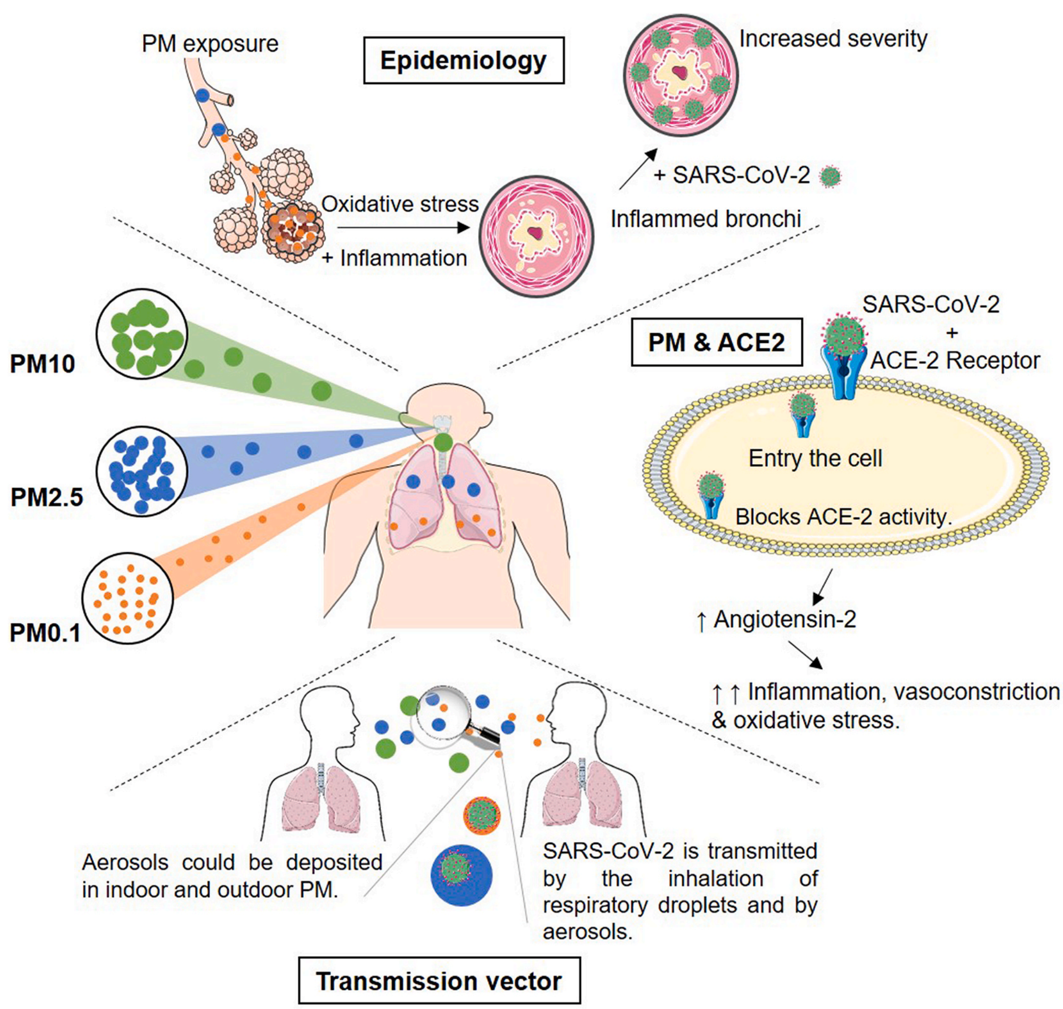

Fig. 1. Role of Particulate Matter in the COVID-19 pandemic.

reach an intercontinental range depending on their size and the atmospheric conditions (Triadó-Margarita et al., 2019). Some diseases have been associated with tropospheric wind patterns or with the presence of airborne dust of desert origin (Jorquera et al., 2015).

Numerous epidemiological studies have analyzed the effects of PM, depending on its size, both in the short and long term, but experimental research has also been carried out to evaluate what happens inside the cell. In these studies, that exposure to high concentrations of particles has been found to alter the production of cytokines and coagulation factors, and cause oxidative stress and genotoxic and mutagenic effects, which explains the associated respiratory and cardiac symptoms (Marquès and Domingo, 2021; Valavanidis et al., 2008).

3. Particulate matter, vulnerability and susceptibility to COVID-19

Epidemiological studies have described an association between air pollution and hospitalizations, especially for respiratory diseases (Pansini and Fornacca, 2021; Almetwally et al., 2020; Guan et al., 2016; Santurtún et al., 2017). Furthermore, it is estimated that PM2.5 causes 400,000 premature deaths per year in the countries of the European Union (excluding Turkey) (eport No 9/2020. The, 2020). With this context, it is worth considering whether exposure to air pollutants can increase the susceptibility and severity of COVID-19.

Different authors have found a statistically significant relationship between PM levels and SARS-CoV-2 infection in certain geographic areas (Jiang et al., 2020; Li et al., 2020; Fattorini and Regoli, 2020; Linares et al., 2021; Travaglio et al., 2021).

The first evidence emerged in China where Zhu et al. analyzed pollution levels in 120 cities and found that there was a relationship between exposure to PM and new daily cases of COVID-19. Specifically, they found that an increase of 10 $\mu g/m^3$ (lag0-14) in the concentration of PM2.5 and PM10 was associated with an increase of 2.24% (95% CI: 1.02–3.46) and of 1.76% (95% CI: 0.89–2.63) in confirmed cases, respectively (Zhu et al., 2020).

Likewise, between January 1 and April 30, 2020, Zoran et al. (2020) performed a study in the Lombardy region in northern Italy, and concluded that high levels of air pollution and specific weather conditions have a significant impact on increasing the infection rate by SARS-CoV-2. The authors explain that the high number of new daily confirmed COVID-19 cases in Milan was correlated with PM air pollution. The pollutants at the beginning of the year exceeded the thresholds recommended by the WHO to protect the health of the population and this could generate bronchial hyperresponsiveness and inflammation (which could also be generated by the usual air contamination in the area); The researchers suggest that exposure to increasing levels of air pollution by particles before and during the pandemic could make the inhabitants more susceptible to viral infection and explain the results found (Zoran et al., 2020).

There are studies that have focused on long-term effects (Wu et al., 2020), for example Coccia et al. (2020) using data analyzed in 55 Italian provincial capitals, found an association between exceeding the limits established for PM10 in previous years and the detected cases of COVID-19 (Coccia, 2020).

On the other hand, some researchers have evaluated the clinical severity or fatality after infection according to the quality of breathing air. A project that worked with data from 9 Asian cities shows that previous exposures to high levels of PM2.5 over an extended period are significantly correlated with current mortality from COVID-19 (Gupta et al., 2020). Similar results have been described in the US, where they found that an increase of 1 $\mu g/m^3$ in the long-term average exposure to PM2.5 was associated with an 11% increase in the death rate from COVID-19 (Mantecca et al., 2009).

Along these lines, Aloisi et al. (2021) carried out an ecological study in Italy with the aim of evaluating the possible association between the concentration of PM2.5 and the mortality rate due to Covid-19 throughout 2020. Although they found a relationship, they did specify that among the confusion factors, meteorological variables played a very important role (Aloisi et al., 2021), something that has also been highlighted in other works (Sera et al., 2021; Srivastava, 2021; Islam, 2021; Yuan, 2021).

There are very many epidemiological articles published over the last 2 years and Marquès and Domingo have recently carried out an exhaustive review analyzing the results obtained in different continents, countries and regions, with significant differences in geographical, meteorological and socioeconomic conditions, and concluding that there is a significant association between chronic exposure to various outdoor air pollutants, including PM10 and PM2.5, and the incidence/risk and severity/mortality of COVID-19 cases (Marquès and Domingo, 2021).

However, several works discuss the necessary caution in the interpretation of the results due to the complexity of the statistical models, the lack of knowledge about many of the risk factors for the disease (which may not be considered as confounding factors in predictive models), the quantification of cases during 2020 (Almendra et al., 2021), as well as the specific terminology which is not always clearly consistently used by researchers (such as the terms: 'particulate matter', 'atmospheric aerosol particles', 'air pollutants', and 'atmospheric aerosols') (Ishmatov, 2021).

Regarding the possible mechanisms that would explain these results, it should be noted that the cells of the respiratory tract are the "entry point" of PM, as well as the first target of respiratory viruses. After exposure to PM, two mechanisms are induced in the lungs: oxidative stress (both by the presence of free radicals among the compounds of some particles and by the production of free radicals in response to exposure to PM) and alteration of the immune response with inflammation (Martin et al., 2021) and inactivation of macrophages (Kaan and Hegele, 2003). This cellular condition facilitates the attack of the virus and increases the severity of viral infections in exposed subjects.

Moreover, this relationship with pollution could also be explained through indirect mechanisms; the composition of the atmosphere (the levels of contamination) at a given time along with certain meteorological conditions could favor a longer permanence of the virus in the air, thus enhancing its spread; for example, it has been described that anticyclonic conditions, and therefore greater atmospheric stability, are related to the increase in Covid-19 cases (Sanchez-Lorenzo et al., 2021).

4. Particulate material as a transmission vector of SARS-CoV-2

The transmission factors and the environmental conditions that favor the spread of a viral infection need to be known to stop a viral outbreak and develop effective preventive strategies. SARS-CoV-2 is transmitted by the inhalation or contact with a susceptible individual's eyes, nose or mouth of respiratory droplets or particles from the air exhaled by an infected person, and by aerosols, a mechanism that, although initially questioned, is currently considered one of the main routes of contagion (Greenhalgh et al., 2021).

According to different studies, these aerosols in the form of liquid microdroplets containing the virus could be emitted by infected people when talking, shouting or singing, and would remain suspended due to their small size and potentially inhaled by other people present in the same area, even at a distance of several meters (Greenhalgh et al., 2021; Lednicky et al., 2020; Stern et al., 2021); alternatively, they could also be deposited in other particles in suspension, of natural but especially of anthropogenic origin, that are part of the basal indoor and outdoor PM. This hypothesis was initially formulated because cities highly affected by the pandemic (such as Wuhan and areas of northern Italy) are densely populated and heavily industrialized areas that annually register high levels of PM (Stern et al., 2021). Furthermore, based on numerous experimental studies, it is known that biological agents and bioaerosols can be found in PM composition, such as viruses, bacteria, bacterial endotoxins, allergens and fungi (Barakat et al., 2020).

When inhaled, small diameter PM would introduce the biological agents it contains into the body, facilitating the development of the virus within the respiratory tract and causing infection (Ramli et al., 2020).

Some researchers have fine-tuned the methodology to try to check whether SARS-CoV2 is found in particles suspended in the atmosphere in different environments (both outdoors and indoors).

The first published work with this goal was carried out in Bergamo, Italy, where the COVID-19 burden was extremely severe during the first wave, and Setti et al. (2020) collected air samples for 3 weeks from specific filters that captured PM10. SARS-CoV-2 RNA extraction was performed from the filters and up to three highly specific virus genes (E, N and RdRP) were amplified. They discovered that at least one of the three genes of the virus was detected in 20 of the 34 samples (Setti et al., 2020). However, the detection of the virus in the air with the described methodology would simply indicate the presence of the virus but does not provide information on the viability of the virus or the risk of infection (Comber et al., 2021).

While in the work carried out in Italy PM was sampled in outdoor environments, Liu et al. (2020) (Liu et al., 2020) developed a study collecting particle samples inside two hospitals in Wuhan during the initial COVID-19 outbreak (between February and March 2020). The concentration of SARS-CoV-2 RNA in PM was high in patient room bathrooms, but low in isolation rooms and bedrooms. In addition, a higher concentration of RNA was generally detected in healthcare personnel areas than in patient areas. It should be noted different samplings were taken over the course of the study, and the implementation of rigorous disinfection procedures led to a marked reduction in the concentration detected (Liu et al., 2020). Other studies also carried out in hospitals reached similar results (Nor et al., 2021; Guo et al., 2020; Chia et al., 2020). In other indoor environments, a recent study in Iran in which 36 air samples were collected in a dental clinic found SARS-CoV-2 RNA in 13 of them (Bazzazpour et al., 2021). Along the same lines and in the same country, the presence of SARS-CoV-2 has been investigated in the air of public places such as shopping centers, a post office, banks, governmental offices, and public transportation facilities including an airport, subways, and buses. In 64% (62% and 67% from the public places and transportation, respectively) of the collected samples, SARS-CoV-2 RNA was detected (Hadei et al., 2021).

However, there are also studies with negative results, both in indoor and outdoor sampling. Regarding the latter, Linillos-Pradillo et al. (2021) (LinillosPradillo et al., 2021) evaluated the presence of virus RNA in PM samples (PM10, PM2.5 and PM1) taken in outdoor air in Madrid, Spain, where, at the time of sampling (May 2020), 28.5% of all cases detected in Spain were accumulated. The month of April, in general, was rainy and windy, with high relative humidity, while the temperatures remained within normal ranges for that moment of the year. These atmospheric conditions caused a situation of good natural ventilation, reducing the levels of atmospheric pollution. In May, there were two outbreaks of Saharan dust, increasing the concentration of PM10, although the daily average values were not as high as at other times of the year in the metropolitan area. The results of this study were negative: no SARS-CoV-2 genetic material was found in the external filters (LinillosPradillo et al., 2021).

The absence of RNA in the samples could be due to different factors. On the one hand, the limitations of movement and socio-economic activity due to the state of alarm in the city would cause a reduced circulation of SARS-CoV-2; on the other hand, the atmospheric and meteorological situation could also cause the dispersion of PM, reducing its concentration in the air. Likewise, the sensitivity of the RNA extraction technique from filters can affect the results.

In indoor sampling, air samples collected inside hospitals in Iran were negative for viral RNA, both from infected patient rooms (Faridi et al., 2020), and from selected wards, such as emergency rooms, ICUs and laundries (Masoumbeigi et al., 2020).

SARS-CoV-2 RNA was also not detected in the air samples collected by Conte et al. (2021) in different community indoors (one train station, two food markets, one canteen, one shopping center, one hair salon, and one pharmacy) in three Italian cities (Venice, Bologna, and Lecce) at the peak of the second wave of the pandemic in that country (Conte et al., 2021).

A systematic review by Maleki et al. (2021), in which discordant results between studies were described, suggested that the effectiveness of PM in transmitting the virus may result from differences in composition among the various locations (Maleki et al., 2021).

There is consensus that more studies should be carried out during new disease peaks, in the presence of increased viral circulation and higher PM concentrations, to gather new evidence. Furthermore, the sampling methodology for PM10, PM2.5 and PM1, as well as the laboratory procedures, should be standardized to be able to compare results between different research groups.

The fact that the virus may be transmitted by PM could have important implications for public health decision-making (Comber et al., 2021). Although, as indicated, there is no agreement on the transporting role of the particles, and it is necessary to optimize the study methods in the laboratory and to verify the viability of the virus (there are still very few published studies (Lednicky et al., 2020; Lednicky et al., 2021), and with small samples), there is an increasing number of works with positive results, although mainly focused on indoor PM samplings (Nor et al., 2021; Guo et al., 2020; Chia et al., 2020; Bazzazpour et al., 2021).

5. ACE-2, particulate matter and COVID-19

ACE-2 is a membrane enzyme found in the lungs, arteries, heart, kidneys, and intestinal cells, and regulates blood pressure by catalyzing the cleavage of the vasoconstrictor peptide Angiotensin 2 into Angiotensin 1-7 which, instead, is a vasodilator and anti-inflammatory molecule (Hayashi et al., 2010).

The activation of ACE-2 can reduce the severity of lung damage by inhibiting both the inflammatory response and oxidative stress. ACE-2 can, in fact, inhibit the intracellular signal of factor NFKB (pathway that activates the inflammatory response) and activate that of factor NRF2 (pathway that activates the anti-inflammatory response), as a protective mechanism against oxidative stress (Fang et al., 2019).

SARS-CoV-2 is characterized by the presence of proteins in its crown that allow it to bind to ACE-2 receptors in cells. The virus enters cells by endocytosis and infects them. The binding of the virus with ACE-2 blocks its activity and therefore, secondarily, causes a higher concentration of Angiotensin 2, vasoconstriction, and lung damage (Pérez et al., 2020).

Some authors have hypothesized that, because age leads to an increase in blood pressure, as a compensatory response, our body expresses a greater amount of ACE-2 in cell membranes to respond to this effect; this would also increase the accessibility of SARS-CoV-2 (Comunian et al., 2020), block the activity of the enzyme and alter the immune defense and protection against inflammation, which would be one of the causes of the greater clinical severity of the infection in elderly people.

Regarding the link between ACE-2, poor air quality and COVID, Paital and Kumar (2020) have suggested that air pollution could activate the expression of ACE-2 in the respiratory cells of human hosts; under conditions of high contamination, an overexpression of the enzyme has been found, which has been related to a greater possibility of infection by respiratory pathogens (including COVID-19) (Paital and Agrawal, 2020).

On the other hand, an experimental work carried out by Lin et al. (2018) evaluated the acute lung damage induced by exposure to PM2.5 in animal models under a condition of ACE-2 deficiency and concluded that the absence of this enzyme hinders the repair of injuries caused by exposure to PM2.5 and decreases the inflammatory response and tissue remodeling. These authors suggested that ACE-2 can protect the respiratory system from pollution-induced injuries (Lin et al., 2018).

In conclusion, SARS-CoV-2 binds to ACE-2 in order to access and enter the cell. Contamination could favor the expression of this enzyme, which would facilitate the entry of the virus. In addition, SARS-CoV-2 would inactivate the function of ACE-2, which would prevent it from carrying out its vasodilator and anti-inflammatory action on the lungs. This would make lung damage more severe, and even more serious in the presence of pollutants. However, there are very few studies on this topic, and new experimental work is necessary to determine its role at the molecular level.

6. Conclusions

Knowing COVID-19's risk factors and SARS-CoV-2 transmission routes is a global priority, both because this virus has caused a pandemic of worldwide extension and very rapid spread, and since it triggers severe symptoms, affects various organs over a prolonged period and has high associated mortality.

Exposure to small diameter PM has been linked to newly diagnosed cases and to the clinical severity of people infected by SARS-CoV-2, which is explained by the oxidative stress and the inflammatory response generated by the particles when accessing to the respiratory system, as well as by the role of PM in the expression of ACE-2 in respiratory cells of human hosts.

Finally, there are more and more studies that detect the presence of virus RNA in PM in indoor environments, which suggests that PM could act as a vector for SARS-CoV-2. However, there is still little evidence to confirm that the microdroplets generated by an infected person can be deposited in the basal PM of outdoor environments. Better knowledge of this transmission route should be a study priority given that, if it is confirmed, PM from outdoor environments could act as a vector of transmission, and therefore prevention strategies should be adapted accordingly. Furthermore, should PM be confirmed as a SARS-CoV-2 vector, the presence of the virus in PM in outdoor environments could be used as an indicator of viral load in a specific area.

Author contributions

Ana Santurtún: Conceptualization; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. **Marina L. Colom:** Investigation; Resources; Writing - original draft. **Pablo Fdez-Arroyabe:** Resources; Validation; Writing - review & editing. **Álvaro del Real:** Investigation; Resources; Visualization. **Ignacio Fernández-Olmo:** Resources; Writing - original draft; Writing - review & editing. **María T. Zarrabeitia:** Conceptualization; Supervision; Writing - original draft; Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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