Environmental Research 204 (2022) 112054

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Airborne magnetic nanoparticles may contribute to COVID-19 outbreak: Relationships in Greece and Iran

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ARTICLE INFO

Keywords:
Particulate matter
Iron-bearing nanoparticles
Airborne
COVID-19
Pandemics

ABSTRACT

This work attempts to shed light on whether the COVID-19 pandemic rides on airborne pollution. In particular, a two-city study provides evidence that $PM_{2.5}$ contributes to the timing and severity of the epidemic, without adjustment for confounders. The publicly available data of deaths between March and October 2020, updated it on May 30, 2021, and the average seasonal concentrations of $PM_{2.5}$ pollution over the previous years in Thessaloniki, the second-largest city of Greece, were investigated. It was found that changes in coronavirus-related deaths follow changes in air pollution and that the correlation between the two data sets is maximized at the lag time of one month. Similar data from Tehran were gathered for comparison. The results of this study underscore that it is possible, if not likely, that pollution nanoparticles are related to COVID-19 fatalities (Granger causality, $p < 0.05$), contributing to the understanding of the environmental impact on pandemics.

1. Introduction

Direct person-to-person transmission, which generally requires prolonged face-to-face or other close contact, is believed to be the most common route for the spread of infectious diseases, although airborne transmission over longer distances cannot be ruled out (Al Huraimel et al., 2020; Wang et al., 2021). This is in addition to the significant public health threats posed by air pollution, especially the fine <2.5 μm particulate matter ($PM_{2.5}$) which, due to their small dimensions, can penetrate deep into the lungs and access the brain and the cardiovascular system, causing oxidative stress and inflammation (Cachon et al., 2014). Interestingly, this somehow parallels the symptoms of SARS-CoV-2 infection in humans. In this regard, the COVID-19 pandemic has offered the opportunity to conduct an intensive examination of virus transmission through PM carriers, also considering the real world features, which has come with many surprises. For example, despite the fact that nearly one in four individuals in India tested positive for antibodies to SARS-CoV-2 in December 2020 (Murhekar et al., 2021), and about 10% of India's population were vaccinated at the time, the extraordinary surge in cases from March 2021 onwards took most analysts off guard, as everyone thought India was doing well and would escape a deadly second wave. On the contrary, based on environmental pollution facts it was expected that "(in India) the number of daily new deaths will peak again during the turning of the year" as mentioned in a preprint on December 11, 2020 [see supplemental file in (Martinez-Boubeta and Simeonidis, 2020). Sadly, the truth turned out to be as predicted. Hence, this paper revisits our previous discussion of the finding that air pollution Granger causes COVID-19 deaths.

In this context, a large body of literature has consistently shown an association between PM and an increase in the numbers of deaths from cardiopulmonary disease, especially among the elderly and those with comorbidities (Seaton et al., 1995), with more than 3 million mortalities per annum (Anenberg et al., 2010). It has been also suggested that air pollution is an important cofactor increasing the risk of mortality from coronavirus. For instance, analysis of the first severe acute respiratory syndrome coronavirus SARS-CoV-1 outcomes in 2003, demonstrated that in heavily polluted regions the risk of dying from the disease was >80% higher compared with areas with relatively clean air (Cui et al., 2003; Kan et al., 2005). Furthermore, a correlation -but not necessarily a causal link-between exposure to NO_2 from the burning of fuel and COVID-19 cases has been reported (Ogen, 2020; Liang et al., 2020). Yet, those studies cannot rule out the possibility that NO_2 is serving as a proxy for other PM vehicle pollution such as soot and metal particles. In this regard, we (Kermenidou et al., 2020) and others (Petrovský et al.,

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https://doi.org/10.1016/j.envres.2021.112054
Received 21 June 2021; Received in revised form 9 September 2021; Accepted 9 September 2021
Available online 20 September 2021

2013), have provided evidence for the ubiquitous presence of magnetite in PM. Iron oxide nanoparticles may pose a potential threat, as they have been frequently and consistently associated with reactive oxygen species (ROS) activity and inflammatory cytokine release (Saffari et al., 2014). Moreover, the increased mutagenic activity of PM extracts related to the presence of magnetite may have a great effect on virus infectivity (Morris et al., 1995). Iron overload is a risk factor for many viral infections (Drakesmith and Prentice, 2008), and probably one of the most important predisposing conditions for many co-morbidities associated with severe COVID-19 (Whiteside and Herndon, 2020). Thus, constituting a biologically plausible pathway through which airborne magnetite may impact SARS-CoV-2 transmission.

On the other hand, while there has been ample evidence for a relationship between long-term air pollution exposure and the severity of COVID-19 outcomes (Pozzer et al., 2020; Cole et al., 2020; Hou et al., 2021), one aspect that has yet to be described is the effect of seasonal variances on excess mortality from COVID-19. This is of paramount importance since reinfections by other seasonal coronaviruses occur most frequently every 12 months (Edridge et al., 2020), and SARS-CoV-2 might share this feature. Therefore, one key question that needs to be assessed is whether air pollution showing seasonal variations is capable of modulating COVID-19 severity in different regions.

On the heels of our previous article, here we aim to investigate the effects of seasonal exposure to $PM_{2.5}$ on the impact of pandemic waves. To the best of our knowledge, it is the first evidence provided on the linkage between air pollution and the seasonal variability of COVID-19.

2. Methods

The major hypothesis of this work is that seasonal patterns of PM, along with certain climatic conditions, can be the main driver of the global pandemic. Consequently, the pandemic's impact was investigated from two perspectives, considering different seasonality and considering different polluted areas. First, we investigated qualitatively the spread of disease in a medium-sized city in Europe, using Thessaloniki, Greece, with over 1 million inhabitants, as an example. Since the effects of PM are related to their chemical composition and size, we focused on the magnetic properties of $PM_{2.5}$. Next, a mathematical model was employed to quantify the association between the COVID-19 outbreaks and air pollution in Tehran, with a population above 10 million, the largest city in West Asia.

Estimation of exposure of inhabitants of Thessaloniki to airborne magnetite was determined by a combination of magnetic measurements and electron microscopy, as described in detail elsewhere (Kermenidou et al., 2020). Briefly, aerosol samples were collected on PTFE $PM_{2.5}$ filters by a low-volume sampler. The filters were weighed before and after sampling using an analytical balance after stabilizing in constant temperature and humidity. Dust particles were characterized by scanning electron microscopy and the average elemental analysis was obtained by Energy Dispersive X-ray Spectroscopy. The filters were cut into pieces and some parts rinsed in a mixed solution of acetone and polyvinyl alcohol in order to collect the magnetic fraction by means of permanent magnets. Samples were drop casted onto a carbon coated copper grid for observation by high-resolution transmission electron microscopy (TEM). Quasi-static magnetic properties were measured using a superconducting quantum interference device. Seasonal arithmetic mean concentrations were calculated over the period from February 2015 to October 2018.

Because the composition and health risks of $PM_{2.5}$ might vary widely in different geographical and climatic areas, a complimentary statistical analysis was performed on data from Tehran, based on Nabavi et al. (2019). The monthly pattern of $PM_{2.5}$ mass concentrations during the period (2011–2016) was compared to confirmed deaths from COVID-19 in Iran, as reported by the "Worldometer" website, updated with daily frequency (https://www.worldometers., 2020). It must be said that epidemiological data were not available at city level. The time-series data were interpolated to evenly spaced observations (Dean and Dunsmuir, 2016). Lead-lag relationships were investigated by cross-correlation analysis of monthly data during the period from March to October. Granger causality was computed by testing the null hypotheses in the Free Statistics Software from Wessa.net (Wessa, 2016).

3. Results

Magnetic traces were identified on in vivo human nasal swab specimens collected in late autumn 2019 from patients in the Otorhinolaryngology Clinic of the General Hospital "Papageorgiou" (Kermenidou et al., 2020). The magnetically responsive PM is made of aggregates in which particles with rounded morphology and a mean size around 15 nm (inset in Fig. 1) appear basically made of magnetite (and minor contribution of Fe^{3+} rich shell and substituted heavy metals such as Cr, Mn, Co or V).

These are particles derived from combustion (Lighty et al., 2000), typically for relative humidity conditions below 65% (Willeke and Whitby, 1975), which, given their tiny size, remain airborne for a long time (Stadnytskyi et al., 2020), and can penetrate the respiratory tract down into the alveolar space (Tellier et al., 2019), where ACE2 is highly expressed. Thereby, magnetite could then tentatively offer a Trojan horse docking for virus infectivity, potentially facilitating its transmission efficiency (Godri Pollitt et al., 2020). In fact, recent studies revealed that iron oxide nanoparticles may interact efficiently with the SARS-CoV-2 spike binding proteins (Abo-zeid et al., 2020). In support of this hypothesis are findings that viable SARS-CoV-2 aerosols, from hospitals in Wuhan (China), were mainly found in the submicrometre <0.5 μm aerodynamic diameter range (Liu et al., 2020).

In this framework, it was analyzed whether the chronic seasonal exposure to airborne magnetite has positive qualitative effects on coronavirus mortality. Results for Greece are shown in Fig. 1. Visual inspection suggests that COVID-19 death rates, up to the end of October 2020, mimic the same lagged pattern in magnetic $PM_{2.5}$ over the past years. Two main conclusions can be drawn from this chart: first, given the epidemiological situation, schools re-opening on 14th September brought a significant negative impact. The figure above (Fig. 1) shows that the country was making progress in bringing down the curve of new

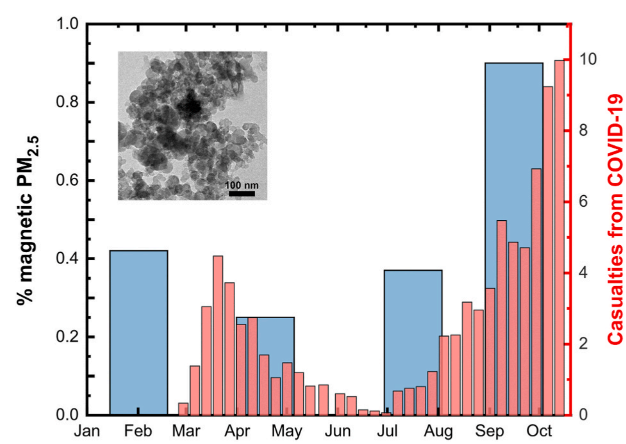

Fig. 1. The disease progression timeline and the seasonal variability of the airborne magnetite pollutant. The thin red bars represent the 7-period moving average for new daily confirmed deaths from COVID-19 in Greece. Note that there is about a four weeks delay from first symptoms after infection to death. The thick blue bars depict the percentage of magnetic material estimated from $PM_{2.5}$ observations at urban site in Thessaloniki, representatively for the years 2015–2018. The inset shows a representative TEM image of the magnetic dust. We ascribe these particles to high-temperature anthropogenic processes, e.g. industrial and traffic sources, but can also result from natural fires, desert dust plumes and cosmic flux. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

deaths from coronavirus until families returned to the big cities from their summer vacation and, consequently, air pollution peaked. Statistical and dynamic modelling approaches have shown that school closures can substantially help reduce the burden of viral diseases (Adda, 2016; Davies et al., 2021). This is consistent with reported increased risks of infection in households with children (Harris et al., 2021). It also adds to evidence that adolescents can seed clusters of COVID-19 cases (Schwartz et al., 2020).

Secondly, the air pollution conditions may had been favourable for the virus circulation since late September 2019, much earlier than the first reported cases. In this regard, we note that WHO declared the pandemic on March 11, 2020. Officially, a 38-year-old woman who returned to Thessaloniki from Milan by air on February 23, 2020 became Greece's first coronavirus. Though, a growing body of evidence suggests that the new SARS-CoV-2 virus had already been circulating unnoticed in the community a few months before the first reported case in Wuhan City, China, by December 2019 (van Dorp et al., 2020).

It is also worth noting that during the winter and spring times the mean $PM_{2.5}$ concentration in Thessaloniki exceeds the European ambient air quality standard of 25 μg/m^3 (Kermenidou et al., 2020). It would mean that the attributable fraction of COVID-19 mortality due to the long-term exposure to ambient fine particulate air pollution could be as high as ~50% (Pozzer et al., 2020). Even though the present data must be interpreted with caution, the amount of airborne magnetite, which is at its peak during the autumn, might potentially explain the rise in the incidence of the second wave of the pandemic outbreak. Concomitantly, magnetic particulate matter shows maximum values during autumn months (0.8 % wt.), compared to <0.4% in spring, meaning that doubling the concentration of airborne pollutants leads to a ten-to 20-fold increase in the number of deaths linked to COVID-19. This goes in line with other studies, which have found that the association between the pollutant and the health outcome is log-linear (Schwartz et al., 2008; Borro et al., 2020; De Angelis et al., 2021). Consequently, our research strongly suggests that magnetic parameters can be used as an efficient proxy to assess the urban atmospheric quality and the impact of COVID-19 in Thessaloniki, and potentially in any other region in the world. Therefore, further investigations focusing on the development of COVID-19 outbreaks over highly polluted areas are encouraged.

In this respect, it should be noted that deaths from COVID-19 vary markedly across countries and at different paces. Changes in the geographical and temporal distribution of disease occurrence may occur as impact of both the concentration and composition of the $PM_{2.5}$ mixture. For example, in a worldwide cross-sectional and longitudinal data analysis Damialis et al. (2021) hypothesized that airborne pollen concentrations could explain the SARS-CoV-2 infection rate variability, however, such correlations are only evident during springtime, when high concentrations of tree pollen occur, but cannot explain the several outbreaks in a year. It is most likely that the contents of water-soluble metal ions in $PM_{2.5}$ compromise the viability of human lung cells by modifying the ROS and inflammatory cytokines response (e.g. representative TNF-α and IL-6) (Pang et al., 2020), thus facilitating the virus infection. A paradigmatic example is the occurrence of elevated $PM_{2.5}$ levels over the Po Valley, Italy, for the 12-days period preceding the pandemic onset (De Angelis et al., 2021).

For the while let us, for the sake of History, focus on Iran since the ancient Persian and Greek cultures intermingled when Alexander the Great conquered most of that region by 330 BC. This may further be related to genomic results demonstrating similarities in the populations of Neolithic Iran-like ancestry and Helladic Bronze Age culture (Clemente et al., 2021). Interest arises from the fact that, when it comes to number of new deaths per day, the third wave of coronavirus in Iran is the worst yet (Fig. 2). But most importantly for our discussion is that the climate in Thessaloniki is warm and temperate (Köppen climate classification: Cfa) due to its proximity to the sea, while Tehran has a cold semi-arid steppe climate (Köppen climate classification: BSk), typically

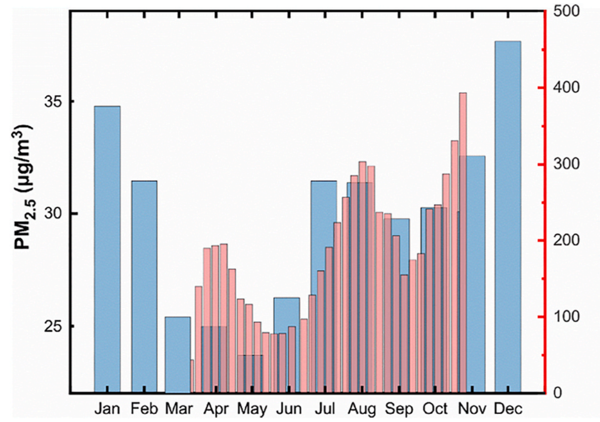

Fig. 2. Two or more 'camel humps' in Iran. The thick blue bars depict the monthly pattern of $PM_{2.5}$ mass concentrations during the period (2011–2016) in Tehran. The thin red bars represent the 7-period moving average for new daily confirmed deaths from COVID-19 in Iran, as of October 28, 2020. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

found at some distance from the sea. On this matter, Iran as a developing country is facing severe problems in terms of air quality. Urban air pollution due to $PM_{2.5}$ in Tehran and other regions of the country has been reported by many researchers (Nabavi et al., 2019; FarajiGhasemi et al., 2020; Hadei et al., 2020; Zallaghi et al., 2020; Kermani et al., 2020). Accordingly, most cities in Iran have $PM_{2.5}$ concentrations above the WHO air quality guideline value, which in turn are magnified by frequent desert dust storms during the summer months as temperatures rise and rainfall reaches a minimum (Shahsavani et al., 2020). However, the highest amounts of $PM_{2.5}$ are normally recorded during winter. The increase of PM concentration in the cold period of the year is due not only to the increased emissions from additional sources, such as domestic heating, but rather also to the decrease in the thickness of the mixing layer (Murthy et al., 2019). These episodes may result in notable health consequences. As such, the highest number of deaths due to exposure to fine particles was estimated to occur in Iran's largest city, Tehran, where motor vehicles play a major role (Oroji et al., 2018; Broomandi et al., 2020). Other episodes that may be linked to human activity include the significant drop of PM in the spring caused by Tehran's minimal traffic flow during Nowruz holidays. Consequently, we assume that the mean seasonal concentrations of magnetite would roughly track the trends in $PM_{2.5}$ levels.

The figure above (Fig. 2) depicts that the coronavirus casualties follow the seasonal variation of air pollution closely, except that the $PM_{2.5}$ waves start sometime early. This plot is of special interest since the data can be used to validate the causal association between pollution and COVID-19 severity. Techniques exist for establishing the direction of this association and have previously been used primarily in fields such as econometrics (Granger, 1988). For instance, to say "one variable X Granger causes another variable Y" means that past values of X contain information that helps better predict future Y rather than just using past values of Y. Therefore, the prediction of Y is significantly improved by including X as a predictor. Let Y = *daily deaths* be the potential outcome in the population of a country exposed to X = *pollution concentration*. The Granger causality was computed under the assumption that the null hypotheses of X does not Granger-cause Y, and vice versa, are true. The F-test and its associated p-value are presented in Table 1.

There is a remarkable correlation between the two datasets. Accepting a lag of one month, the correlation coefficient >0.7, which is reasonable given that there are significant delays between infection, the onset of symptomatic disease, and recovery or death. These estimates imply that people who died this week were most likely infected a month ago (Sanche et al., 2020). In the same fashion, it is assumed it would take

Table 1
Iranian values of the constructed proxies for $PM_{2.5}$ pollution (X) and the health impact (Y) on COVID-19, and both cross-correlation and Granger causality summaries identifying significant causal relationships between X→Y. Significance level **$p < 0.05$.

X	Y	lag	ρ(Y [t], X [t + lag])
25	65	−4	−0.12
23.7	140	−3	0.10
26.3	74	−2	0.53
31.5	98	−1	0.71**
31.4	199	0	0.51
29.8	223	1	0.16
30.3	159	2	0.04
30.1	262	3	−0.27
Granger-Causal		Y = f(X)	X = f(Y)
F		8.33	0.04
P		0.04	0.86

a month before any effect of vaccination on deaths is observed (England and Public Health. I, 2020).

Moreover, this analysis suggests that the $PM_{2.5}$ level is predictive of the subsequent SARS-CoV-2 related deaths: the F statistic was 8.33 and the p-value was 0.04. The null hypothesis that X does not cause Y can be rejected at the 5% significance level. On the other hand, the p-value of 0.86 allows us to accept the null for X = f(Y). The fact that the first hypothesis was rejected and the second was not, means that X can be used to forecast Y. Sensitivity analyses (not shown) using mid-month values on the 15th day, and log-transformed data, found little effect on results. Consequently, it is safe to conclude that a portion of the variability of the clinical outcomes of COVID-19 could be affected by environmentally driven variance of nasal infectivity (Hou et al., 2020).

4. Discussion

4.1. Virus impact and air pollution linkage

This finding is consistent with the result by Sharma et al. (2021), which states that pollutant $PM_{2.5}$ exhibited a statistically significant impact on the Covid-19 deaths among the world's top 10 infected countries (including Brazil, Chile, India, Iran, Italy, Peru, Russia, Spain, the UK, and the USA), from February 1, 2020 through June 30, 2020, while our study includes a more extended timeline.

Moreover, our results indicate that there is a one-way link from $PM_{2.5}$ concentrations to COVID-19 deaths, which is also supported by Delnevo et al. (2020) and Mele et al. (Mele and Magazzino, 2020), who reported that there is a Granger causal relationship between daily $PM_{2.5}$ values and new daily COVID-19 infections in Emilia-Romagna, Italy, and a similar linkage between $PM_{2.5}$ concentration and COVID-19 mortality in 25 cities in India, respectively. Another study in Peru shows the higher rates of spread of COVID-19 in Lima were associated with the increasing levels of exposure to $PM_{2.5}$ in the previous years (2012–2016) (Vasquez-Apestegui et al., 2020).

Thus, the relationship to COVID-19 mortality in Iran is not unexpected, considering past evidence of association between patterns of $PM_{2.5}$ mass concentrations and, for example, cases of cardiovascular mortality: a study of the 2008–2017 period showed that 2009 and 2010 were the most polluted and unhealthy years, the lowest being 2014, coinciding with the minimum and maximum of solar cycle 24, respectively (Zallaghi et al., 2020). Incidentally, note that a small amount of iron oxides arrives as cosmic flux (Kapper et al., 2020). In this regard, the dust concentration in ice cores retrieved from Greenland show a modulation with a period of about 11 years all the way back from at least 100,000 yrs BP, which points to the solar cycle (Ram et al., 1997). It is interesting to note that the idea that the Sun influences the weather has been discussed time and again for over a century (Meldrum, 1873). Likely, the solar cycle modulates the solar wind and affects, also, the rainfall and seasonal temperature patterns through alteration of atmospheric circulation on decadal timescales (Leamon et al., 2021), and, therefore, also the dust modulation. Indeed, a recent paper has linked the increasing levels of $PM_{2.5}$ to the worst drought that has hit Taiwan in more than a half-century (Chen et al., 2021). Besides, analysis performed in the summer season during the period 2001–2012 revealed that the largest number of dust storms in southeastern Iran occurred in June 2008, attributed to the influence of specific meteorological conditions as the abnormal enhanced cyclonic circulation over northern Arabian Sea (Rashki et al., 2015). A further confirmation comes from the recent work by Cooper et al. (2021). In fact, both the COVID-19 pandemic and the new solar cycle 25 officially began in December 2019. It is to be seen whether the magnetic state of the Sun can affect $PM_{2.5}$ trends and may play a role in pandemics (Hope-Simpson, 1978; Nicastro et al., 2020; Nasirpour et al., 2021). Although the exact nature of the link cannot be established at present, additional studies are needed to reject the coincidence entirely (Towers, 2017).

4.2. Possible mechanisms

While our study supports a link between a month-lag $PM_{2.5}$ and COVID-19, the mechanisms underlying this relationship are complex, and beyond the scope of this paper. Several studies have previously found similar effects of PM on infectious diseases such as influenza (Chen et al., 2018) and coronavirus outbreaks (Villeneuve and Goldberg, 2020). In a recent review, Domingo et al. (2020) have collected evidence that supports a clear association between concentrations of various air pollutants and the airborne transmission of SARS-CoV-2 and the severity of disease outbreaks. Enhanced persistence of the virus in the air, promotion of a pro-inflammatory state, and increased expression of the viral receptor ACE-2, are all factors that have been proposed as possible links between air pollution and COVID-19 (Borro et al., 2020). Indeed, Watzky, et al. (Watzky et al., 2021) have recently found that many chemicals in PM can regulate ACE2 expression, which is important for SARS-CoV-2 entry into the cells. In parallel, there is consistent, strong evidence that the airborne route is likely the dominant mode of transmission for SARS-CoV-2 (Greenhalgh et al., 2021). Consequently, several studies have been reported that explored the presence of SARS-CoV-2 in the air, both in hospital (Zhou et al., 2020; Chia et al., 2020) and non-medical environments. In particular, Setti et al. (2020) analyzed the outdoor open-air from streets in Bergamo, Italy. In contrast, Hadei et al. (2020) detected viral RNA associated with ambient indoor PM in Tehran's public places and transport vehicles. Both may give support to our findings. Even so, Belosi et al. (2021) estimated very low (<1 RNA copy/m^3) average outdoor concentrations of SARS-CoV-2 in Lombardia, which means a very low probability of airborne transmission provided that large gatherings of people are avoided, though they admit that it could be more relevant for indoor environments due to the combination of virus-laden aerosols and nanometric PM (around 0.01 μm in diameter, like in our case). This parallels the well-established pathogenic role of the microbial component of PM (see below) (Griffin, 2007).

By exploiting data from two countries, which differ in several respects, it was possible to successively infer the potential link. But the association of pandemic outbreaks with different PM seasonality in various regions of the world does not prove that PM alone is necessarily the mediating mechanism in COVID-19 lethality. It is possible that these trends are also correlated with other atmospheric variables (Paraskevis et al., 2021), which leaves the possibility of confounding (Ito et al., 2007). For example, Wang and Wang (2021) founded a nonlinear relationship between COVID-19 and air pollutants, and the temperature has a significant impact on the correlation between these two variables. In this regard, it has been speculated that cool and dry weather contributes to the transmission of the Covid-19 pandemic, as it influences socialising patterns and encourages indoor activities (Sharma et al., 2021). At the same time, the relative humidity of the environment has been shown to have a dramatic effect on respiratory droplet transport and evaporation (Dbouk and Drikakis, 2021; Brain and Valberg, 1979). And it was previously suggested that the combination of temperature and humidity modulates the virus survival, transmission and seasonality (Marr et al., 2019). These conditions are particularly dangerous at under 60% humidity and temperatures around 20 °C, also typical for indoors (Biryukov et al., 2020). In addition, sunlight can induce anoxic conditions that stabilize ROS in iron-containing organic-rich aerosol particles, thus affecting the lifetimes of aerosol-bound pathogens and their health-related impacts (Alpert et al., 2021). Also consistent with our findings is the report by Karimi et al. (2020) on the seasonal concentrations of airborne biome and associated $PM_{2.5}$ in Isfahan, the third largest city in Iran. All of these together provide a sound explanation for the positive (negative) relationship between $PM_{2.5}$ concentration with air temperature and relative humidity (the presence of clouds, precipitation, wind speed and UV radiation) observed at Isfahan from March 2019 to March 2020 (Kermani et al., 2020). Correspondingly, the presence of magnetite in PM extracts has been previously shown to strongly correlate also with meteorological data, in particular, the number of sunny hours and the relative humidity (Muxworthy et al., 2001).

On the other hand, Pauluhn and Wiemann (2011) showed that the repeated inhalation exposure to iron oxides cause nonspecific pulmonary inflammation as well as ferritin protein expression, which shows a clear dependence on the particle overload. This is the result of the degradation of magnetic nanoparticles and the natural strategy to limit the toxicity of free iron ions (Kolosnjaj-Tabi et al., 2016), which may act as trigger for infection. In this regard, magnetic characterization data cited in our previous publication can be used to estimate in several μg per day the airborne magnetite inhaled dose (Kermenidou et al., 2020). Though, note that PM inhaled dose is a function of both pollutant concentration and the inhaled volume of air, which depends on individual characteristics, such as age, sex and physical activity (Greenwald et al., 2019). The possibility that elevated iron status aggravates virus infections (e.g. HIV-1 and hepatitis C) is reviewed in Drakesmith and Prentice (2008). Evidence shows that inflammation, oxidative stress and altered iron homeostasis are linked (Orino et al., 2001), and play a potential role in the pathogenesis of COVID-19 (Edeas et al., 2020). This notion is supported by the fact that COVID-19 patients with elevated levels of ferritin are much more likely to experience severe symptoms and possibly increased mortality rates (Casas Rojo et al., 2020; Shoenfeld, 2020; Chaudhary et al., 2021; Burugu et al., 2020; Perricone et al., 2020; Habib et al., 2021). Therefore, it is envisaged that magnetite in PM could participate in most of the typical complications caused by COVID-19.

4.3. Limitations of analysis

Nonetheless, the present study has several limitations that should be considered when interpreting its findings. First, our modelling of 'Granger-Causality' is designed to handle pairs of variables, in which only linear relationships between predictor (pollution exposure) and target variable (casualties) are considered, despite associations between air pollution and health outcome are rarely linear. In addition, it may suffer an inherent limitation if a third variable affects both the exposure and the outcome. For example, climatic factors (such as temperature, rainfall and prevailing winds) exert their effects on the vertical profiles of air pollutants, but also modulates human activities and would subsequently impact the relationship between PM and the spread of infections. As mentioned above, despite the role of the meteorological parameters is quite evident in this study, these have not been quantified. Also, we were unable to assess other important potential cofounders; for example, De Angelis et al. (De Angelis et al., 2021) concluded that pandemic's diffusion patterns and mortality are influenced by a multiplicity of environmental, social and economic indicators, to which other researchers also added dietary (Perez-Araluce et al., 2021) and genetic factors (Vietzen et al., 2021). In particular, Bontempi et al. (Bontempi et al., 2020, 2021; Bontempi and Coccia, 2021) provide further insights into the interplay between international trade data and the impact of COVID-19 in society. In this context, it is important to remember that characteristics that can stand in for environmental-to-human proxies (e.g. data on air pollution) can always be associated with other determinants related to person-to-person transmission; for instance, economic factors, such as the import and export transactions to and from big cities with high population density and intensive transport, can be seen as a reflection of social interactions that leads, concurrently, to higher pollution.

A second limitation of this study is missing data. On the one hand, the detailed identification of the mechanisms underlying this effect is limited by air quality measurement protocols, since to date ultrafine particles (<100 nm) and the occurrence of magnetite in the atmosphere are neither monitored nor regulated (Maher et al., 2020). Another limitation is the spatial resolution of COVID-19 cases, as it was mostly not available at the city level, and inference of the epidemic dynamics at the nationwide level may be misleading and should be taken with care. Furthermore, COVID-19 deaths are probably underreported in almost every country (Institute for Health Metr, 2021). Despite its limitations, reported deaths are likely to be more reliable than new case data. Given the above considerations, future studies are needed involving a larger number of observations.

Indeed, final mention must go to the fact that our results are provisional, based on epidemiological data collected up to the beginning of November 2020, and a comprehensive evaluation will need to follow after the COVID-19 pandemic. These limitations notwithstanding, at the time of revisiting this manuscript -early June 2021- it seems that mortality rates trends follow the same pattern as in the previous year despite the many restrictive measures (masking, vaccines, lockdowns, etc.) put in place in response to the COVID-19 crisis. Indeed, it was widely suggested that staying at home policy did not play a dominant role in reducing COVID-19 transmission (Savaris et al., 2021; Boretti, 2020), nor did it significantly influence $PM_{2.5}$ pollution (Broomandi et al., 2020).

Below, the number of weekly deaths in 2020 is compared with the ongoing pandemic wave (Fig. 3). It suggests that the relationship between PM level and pandemic mortality that we observe is maintained over time. In fact, recent literature has already proposed the use of air pollution data in 2018 to separate the effect of human mobility and control measures in the COVID-19 pandemic during 2020 (Coccia, 2021). In this regard, Edridge et al. (2020) detected evidence that protection against reinfection by all human coronaviruses declined within a year. Obviously, for each epidemic wave, the growth and decay regimes depend on the baseline incidence and the implementation of various lockdown restrictions. However, country-to-country discrepancies in the wave's characteristics are likely due to geographic heterogeneity, being some regions (Greece) in temperate climate with distinct fall and spring blooms, while others (Iran) located in the subtropical region suffer also occasional summer outbreaks. For example, the summer outbreak in Iran (not observed in Greece) from June to September corresponds, and it is at the time when the concentration of PM and bacterial colonies are most prevalent in the ambient air of Ilam, in the western part of the country, due to dust events (Amarloei et al., 2020). It is also very interesting to highlight that the most severe dust transport episodes in Greece usually appear during the spring and autumn, which parallels more or less the advent of COVID-19, while minimum values are observed in the summer due to the prevailing northerly wind patterns (Mitsakou et al., 2008). Another telling example is Saudi Arabia, a country with a hot climate, which has been characterized so far by a single wave per year (Ben Maatoug et al., 2021; https://www.worldometers., 2021). In this regard, a hypothesis has been set that desert dust intrusions have modulated the spreading and virulence of COVID-19 (Rohrer et al., 2020). Those dust outbreaks come loaded with bioaerosols (Griffin, 2007; Polymenakou et al., 2008; Gorbushina et al.,

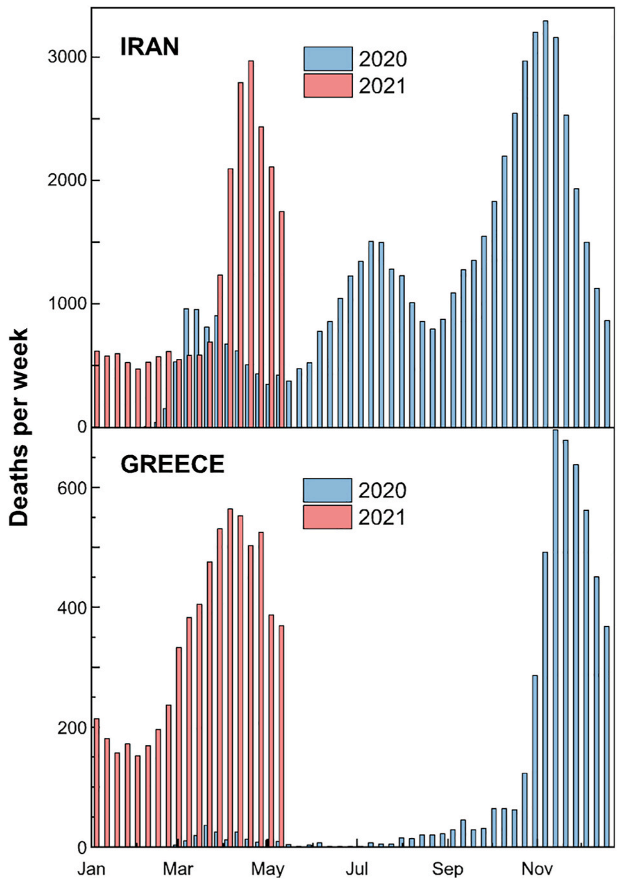

Fig. 3. The weekly counts in 2020 (blue bars) are compared to deaths for the same weeks in 2021 (red bars). Top: In the Islamic Republic of Iran, as of May 24, 2021, there have been 2.855.396 confirmed cases of COVID-19 with 79.056 deaths, and 3.141.577 vaccine doses have been administered (https://covid19.who.int/region/emro/country/ir). Bottom: In Greece, from January 3, 2020 to May 16, 2021, there have been 389.804 confirmed cases of COVID-19 with 11.772 deaths, reported to WHO (https://covid19.who.int/region/euro/country/gr). A total of 4.337.001 vaccine doses have been administered. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2007; Hu et al., 2020), which could possibly have a synergistic impact on human health. And they are aligned with regional weather regimes (as defined e.g. by the summer North Atlantic Oscillation index (Salvador et al., 2014)) that are suspected –again- to be globally coupled to solar activity (Laken and Stordal, 2016).

In contrast, we note that mathematical models of SARS-CoV-2 transmission assume that physical distancing can mitigate pandemics and prevent successive waves, however, once these social measures are reduced, the case-fatality rate will again increase. In fact, using one such model to describe the propagation of COVID-19 in Spain resulted in disparate predictions (Castro et al., 2020). Similar attempts in the Republic of Korea have not really grasped the timing of outbreaks (Kim et al., 2020), leaving us with the impression that the dynamics of the COVID-19 pandemic may be essentially unpredictable. In this sense, we believe patterns of air pollution may further assist in forecasting.

In summary, our analysis identifies that exposure to $PM_{2.5}$ in excess have a significant impact on the development of lethal SARS-CoV-2 infections and provides a quantitative prediction of the link between airborne toxic metals, and concentrations during the previous month, on increased rates of mortality. These findings not only explain large parts of regional and seasonal differences in death rates from COVID-19 but also confirm those of many very recent contributions and call for policies aimed at a rapid reduction in air pollution. It is to be seen whether our initial conclusions remain appropriate and would be relevant to the public health response to future outbreaks.

Credit author statement

C.M.-B. did the conceptualization of the work, the design of the methodology, data curation and evaluation and the writing of the draft. K.S. supported experimental section as well as writing, review and editing of the manuscript.

Contributors

Both authors conceived of the idea for the study. Both authors designed the study. CMB conducted data analysis and drafted the manuscript, which KS critically reviewed.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

All data are available from public repositories, in particular the Worldometers Database (https://www.worldometers.info/coronavirus), referenced studies and/or from the corresponding author on request.

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.

Acknowledgments

We gratefully acknowledge the collaboration of Diego Martinez from DMcreatividad (https://www.dmcreatividad.com) for his contribution to the Graphical Abstract.

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