Article

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Abstract: The possible effect of Particulate Matter (PM_{10} and $PM_{2.5}$ of diameter 10 and 2.5 µm respectively) levels on Covid-19 mortality is now well established. However, time-evolution of Covid-19 mortality according to $PM_{2.5}$ levels has been scarcely investigated. Aim: To understand this relationship at the European level for the period 2020 (beginning) - 2022 (end). Methods: 16 representative locations in Europe (81 million people) with heterogeneous levels of PM2.5 (µg.m-3), from low to high. PM2.5 levels were assessed by various methods, and Covid-19 mortality was reported by Johns Hopkins University. Results: The trend of Covid-19 mortality vs. PM2.5 levels varied among locations. Overall, the estimated mean value was of a 40±20% mortality increase per 1 µg.m-3 PM2.5 increase. The stronger the positive gradient of the PM peak, the stronger the positive gradient of the Covid-19 mortality. Exposure to several PM peaks during about a 2-month period was the main contributor to Covid-19 mortality increases. Conclusion: Our data confirm a temporal relation between PM2.5 exposure and Covid-19 mortality, considering a 2-month integration-time for pollution events. Number-concentrations of PM should be used in the future rather than the PM2.5 mass-concentrations (µg.m-3) with the consideration of PM composition to better explain this finding.

Keywords: COVID-19; mortality; PM2.5; air pollution; Europe

1. Introduction

Ambient air pollution has a large range of negative impacts on human health [1–4], mainly increasing the number and severity of respiratory and pulmonary diseases [5], including infections [6] and the risk of heart attacks and strokes [7,8]. Also, long-term exposure to polluted air can produce perturbations of the immune system [9]. This air pollution concerns mainly airborne Particulate Matter (PM) with particles smaller than 10 µm (PM_{10}), and more precisely smaller than 2.5 and 1 µm ($PM_{2.5}$ and PM_1).

The possible effect of PM_{10} and $PM_{2.5}$ pollution on the Covid-19 (SARS-COV-2) pandemic new cases and mortality was intensively studied from less than a year after the pandemic start, mainly based on the situation in the Lombardy region (Italy) where air pollution levels and the mortality were among the highest in Europe. These studies presented a statistical relation between PM levels and Covid-19 morbidity and mortality during the first phase of the pandemic [10–17]. These conditions first consisted of respiratory and cardiovascular distresses [18] and were indeed related to the immune system [19,20]. Nevertheless, only few studies have investigated the link between PM and Covid-19 mortality at the European level [21].

Although a large number of papers support the existence of a relation between air pollution exposure and Covid-19, one can argue that this correlation could be an artefact due for example to weather parameters. The number of Covid-19 cases was found to be lower during periods of high-speed wind, which dissipates the PM pollution [22,23] studied the correlation between Covid-19 and

weather conditions during the first phase of the pandemic, and concluded that as far as local meteorology is concerned, temperature and humidity are negatively correlated with the number of cases. In winter conditions, PM pollution often increases when temperature decreases, due to heating that produce fine particulates, thus making difficult to decorrelate the various parameters. Nevertheless, the absence of a relation between Covid-19 outbreaks and temperature and UV radiations [24] could suggest that air pollution is indeed the main contributor to Covid-19 spread. In addition, during a long series of observations conducted in France abatement from rain precipitations was observed for particle larger than 10 μm but not for particles 0.2–10 μm [25], thus supporting an intervention of fine PM independent of meteorological factors. A proper role of air pollution is further confirmed by studies in which air pollution and Covid-19 morbidity and mortality were statistically related after adjustment for meteorological variables [18].

All measurements from 32 cities and districts of 6 countries in Western Europe have been combined to show a statistical trend between $PM_{2.5}$ levels and Covid-19 mortality for a period longer than all previous studies, from early 2020 to early 2022 [26]. The authors found an increase of Covid-19 mortality aligned with $PM_{2.5}$ mass concentration increases, leading to a factor 5.5±1.0 % increase in mortality when the pollution increases from 5 to 45 μg.m^{-3}. This corresponds to a mean increase of 10.5±2.5 % of mortality per $PM_{2.5}$ 1 μg.m^{-3}. More precisely, the trend, similar for the 6 countries analyzed, depended on the analysis period and decreased with time from the first spread of the pandemic in early 2020 to the vaccinal race after mid-2021. This mean result is close to previous works showing that a $PM_{2.5}$ increase of 1 μg.m^{-3} can lead to at least an increase of 11% in Covid-19 mortality in the United States [27]. Similar values were found in England [28], in the Netherlands [29], in Northern Italy [30], in Brazil [31] and in a meta-analysis on 35 observational studies [32]. All these studies suggest that the relative effect of PM pollution on Covid-19 mortality is not country-dependent.

A Spearman correlation coefficient of 0.44 was found when analyzing the data in US up to mid-2021 [33]. The Spearman correlation was between 0.45-0.61 for the most affected part of Italy during the first semester of 2020 [14]. A positive correlation of 0.29 was also found in Poland in Spring 2020 [34]. Finally, it has been shown that for the 3 months of 2020 in Wuhan City (China), the Pearson correlation rose to 0.4 considering a lag-time of about 20 days between $PM_{2.5}$ spikes and Covid-19 mortality [35]. These positive correlation values support the hypothesis of a statistical link between $PM_{2.5}$ pollution and Covid-19 mortality.

We propose here a detailed data analysis to better understand such relation by considering 16 representative locations in Europe with mean $PM_{2.5}$ levels from low to high for a total of 81 million people. This work is motivated by the interest first of better evaluating the time-evolution of the relationship between $PM_{2.5}$ and the Covid-19 mortality at different locations in Europe, and second of providing new results on the possible lag-time between the pollution events and Covid-19 mortality and on the effect of the strength and duration of the events.

2. Materials and methods

We consider here the main period of the pandemics, from early 2020 till the end of 2022. As explained before [26], the comparison of the temporal evolution of $PM_{2.5}$ spikes and Covid-19 mortality needs reliable data in order to minimize the statistical bias that irregularly sampled data may generate (such as missing mortality data for several days followed by a sudden data adjustment).

2.1. PM exposure and Covid-19 data sources

$PM_{2.5}$ mass-concentration data were available from different sources. Initial sources were the national air quality monitoring networks, although, because of their operational cost, only few reference stations were available per cities or regions. The other ones were non-official sources with a higher resolution. We consider here the Pollutrack networks in several cities of Europe where measurements are gathered using mobile light optical aerosol counters deployed on rooftops of hundreds of electric vehicles, providing a better spatial coverage of the cities than using just few reference fixed stations [36]. Thus, we averaged all $PM_{2.5}$ daily measurements available in a given

region from the air quality networks, and, when available, from the Pollutrack data that provides a better integration of the hyperlocal PM$_{2.5}$ variability.

To go further than in previous works [26], we now consider the results from 16 locations (cities, regions or countries) for a total of almost 81 million people (Table 1), almost equally representing the most polluted regions in Europe (where reliable Covid-19 data are available) and the regions with medium and low pollution levels, to facilitate direct comparisons. We chose to define "low pollution level" as when PM$_{2.5}$ mean mass concentration during the considered period is below 10 μg.m^{-3} (twice the new annual mean value recommended by the World Health Organization as of September 2021), "medium pollution level" when the mean value is between 10 and 15 μg.m^{-3}, and "high pollution level" when the mean value is higher than 15 μg/m^3 (3 times the WHO recommended annual average). Information on the analyzed locations is presented in Table 1.

For the purpose of this work, Covid-19 mortality data are retrieved from the John Hopkins University datasets (https://coronavirus.jhu.edu/).

We have chosen to stop the analysis at the end of 2022 because the mean Covid-19 mortality decreased in Europe due to vaccination, herd immunity, and the return of the classical seasonal flu and respiratory diseases. On the other hand, the date of the analysis start depends on the availability of Covid-19 data and on the spread of the pandemic. To be able to compare similar effects of the PM$_{2.5}$ level on Covid-19 mortality for the various locations, we have sometimes excluded the period when the pandemic was locally not well managed and where the lockdowns had significantly affected the mortality trend for short time periods. The starting dates of time-period here considered for the 16 locations are given in Table 1.

Table 1. Regions, departments or studied cities, population, source of PM pollution data and level of pollution peaks, time-period considered.

Location Name (Country)	Population (10⁶ Inhabitants)	Source of PM$_{2.5}$ Data	Mean PM$_{2.5}$ Level	Starting Date
Bouche du Rhone (FR)	2.0	Pollutrack	Medium	Mid-Dec 2020
Emilia-Romagna (IT)	4.5	Air quality network	High	Mid-April 2020
Estonia (EE)	1.3	Air quality network	Low	Mid-Dec. 2020
Gironde (FR)	1.6	Air quality network	Low	Mid-March 2020
Hungary (HU)	9.7	Air quality network	Medium	Mid-April 2020
Lazio (IT)	5.9	Air quality network	Medium	Mid-Dec. 2020
Lombardy (IT)	10.1	Air quality network	High	Mid-Dec. 2020
London (GB)	9.0	Pollutrack	Medium	End May 2020
Nord (FR)	2.6	Pollutrack	Medium	Early Jan. 2021
Nordrhein-Westfalen (DE)	17.9	Air quality network	Low	Mid-April 2020
Paris (FR)	2.2	Pollutrack	High	Mid-Dec. 2020
Rhone (FR)	1.9	Air quality network	Medium	Mid-Dec. 2020
Seine Saint-Denis (FR)	1.7	Air quality network	Medium	Mid-Dec. 2020
Toscana (IT)	3.7	Air quality network	Medium	Mid-Dec. 2020
Yorkshire and the Humber (GB)	5.5	Air quality network	Low	Early July 2020
Zuid-Holland (NL)	3.7	Pollutrack	Medium	End July 2020

2.2. Statistical and epidemiological analyses

All the results and the proposed conclusions in this paper are resulting from different classical statistical analysis. First, the Pearson correlation coefficient was used for the temporal evolution Covid-19 mortality with PM$_{2.5}$ pollution levels; lag-times between the two sets of data were also considered as a possibility to increase the correlation. Then we introduced the notion of gradients for temporal evolution of PM$_{2.5}$ and Covid-19 mortally, by calculating at a given time the difference between each value and the value just before, and dividing the results by a temporal window. This

calculation was used to establish a relationship between the slope of the time-evolution of the PM$_{2.5}$ and the Covid-19 mortality. Finally, for all locations, the relationship between these parameters was established by applying linear fits (the data were integrated over dedicated windows to reduce the scatter of the individual values).

As previously proposed [26], mortality data were divided by the population of the location. Then, both mortality and air pollution data were integrated over one week to limit the scatter of daily pollution values and daily variations in the collecting process of the mortality data. A sliding smoothing procedure was applied on 3 consecutive points to reduce the remaining short-term variations of the data. It was then necessary to adjust the time-scale of the two curves, by researching a better time-resolution of the pollution trend when compared to Covid-19 mortality trend. Tests and trial procedures showed that applying a sliding smoothing procedure on the pollution curve was not enough to increase the correlation between the two curves. Thus, we propose a more complex procedure by using two freedom parameters. The first one assumes that the effect of the pollution on Covid-19 mortality is not direct but requires an integration time; a given exposure time to pollution peaks could be needed to significantly irritate the pulmonary system that will consequently become more sensitive to Covid-19. Mathematically speaking, each value of PM$_{2.5}$ pollution was replaced by the mean of the previous PM$_{2.5}$ values during a given time-period, acting as an integration procedure, while the Covid-19 mortality values remain unchanged. The second parameter is a possible positive lag-time between this new PM$_{2.5}$ curve and the mortality curve, which could be related to the lethality of Covid-19 after invading the pulmonary system. These two parameters are adjusted to search for the higher correlation between the two curves.

As the data could be scattered at a given location mainly because of the mortality-reporting uncertainties, in each location air pollution data and their corresponding mortality data at the corresponding time were averaged with steps of about 0.5 µg.m^{-3}; then the linear fit is applied.

3. Results

3.1. Time evolution of PM$_{2.5}$ levels and Covid-19 mortality

As shown in Figures 1a and 2a, PM$_{2.5}$ and Covid-19 mortality curves do not present the same behavior, the air pollution curve being more oscillating than the mortality curve. This could be due to the fact that the mortality evolution is a slower phenomenon than the air pollution evolution that is strongly linked to the short time-scale variations of the meteorological parameters (mainly wind speed).

Figure 1b shows time evolution of PM$_{2.5}$ levels and Covid-19 mortality for the Emilia-Romagna region, exposed to high levels of pollution using weekly integrated data after applying the integration procedure for PM$_{2.5}$ data.
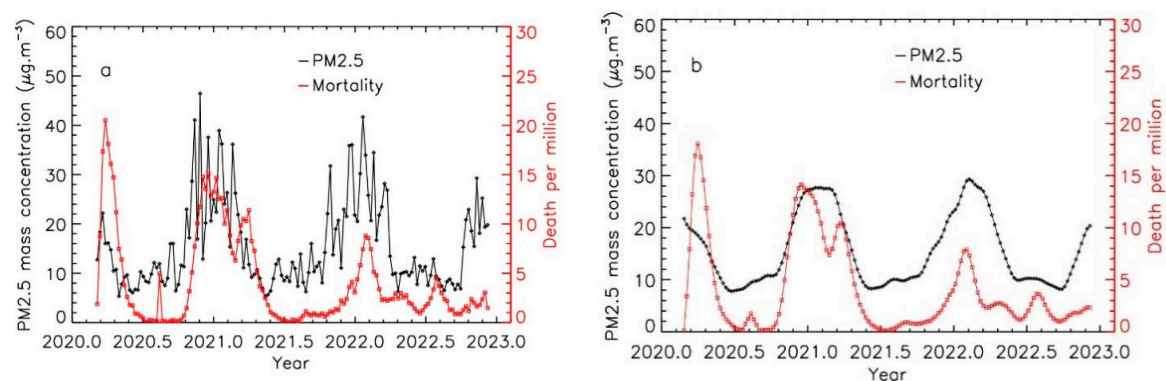
Figure 1. Time evolution of PM$_{2.5}$ levels and Covid-19 mortality for the Emilia-Romagna region, exposed to high levels of pollution; a: weekly integrated data; b: weekly integrated data after applying the integration procedure for PM$_{2.5}$ pollution data.

This procedure applied to increase the correlation between the curves even for cities or regions with low pollution levels like Gironde region is shown in Figure 2b.
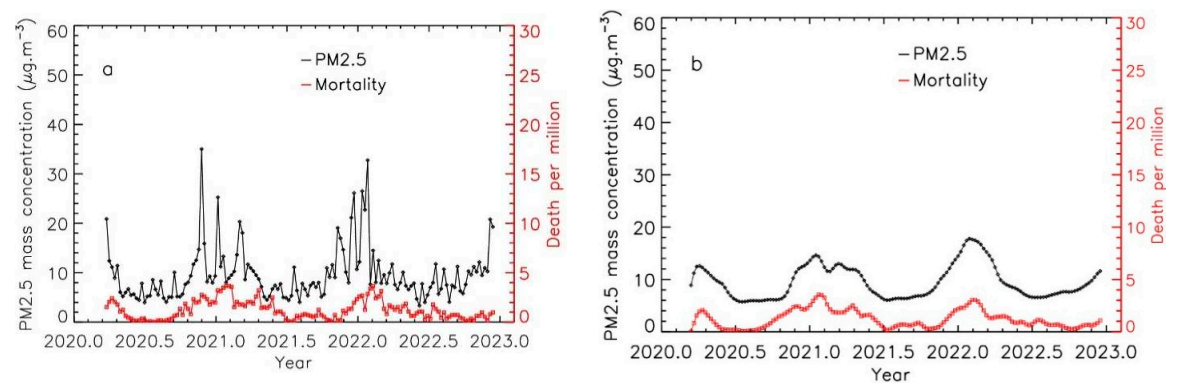
Figure 2. Time evolution of PM$_{2.5}$ levels and Covid-19 mortality for the Gironde region, exposed to low levels of pollution; a: weekly integrated data; b: weekly integrated data after applying the integration procedure for PM$_{2.5}$ pollution data.

The Pearson correlation coefficients before and after applying the first sliding smoothing and the 2-parameters adjustments are given in Table 2. The mean value for the integration is 8.8 ± 2.5 weeks, and the mean value for the shift (lag-time) is 0.7 ± 0.8 weeks. These results could indicate that an exposure of about 2 months to significant pollution peaks is needed to irritate sufficiently the pulmonary system before impacting Covid-19 mortality. These deleterious effects are reversible and are similar for the negative trends (decrease of mortality with pollution dispersion). On the other hand, about one-week shift may indicate the swiftness of virus lethality.

The proposed procedure strongly improved the Pearson correlations for most cases, reaching correlations up to 0.8. Considering the strength of PM$_{2.5}$ spikes and Covid-19 mortality rates that differ from one county to another, the convergence to similar values seems to indicate that these correlations are real and that the proposed procedure can reveal the time effect of pollution on Covid-19 mortality.

Table 2. Regions, departments or cities studied, population, length of the integration (in week) for PM2.5 levels data, and shift (in week) of the Covid19 mortality curve.

Location Name (Country)	Integration Width (Weeks)	Shift (Weeks)	Correlation before	Correlation after
Bouche du Rhone (FR)	7	2	0.56	0.82
Emilia-Romagna (IT)	9	0	0.52	0.76
Estonia (EE)	14	0	0.28	0.60
Gironde (FR)	11	0	0.36	0.81
Hungary (HU)	7	1	0.56	0.83
Lazio (IT)	9	2	0.37	0.79
Lombardia (IT)	9	0	0.47	0.78
London (GB)	8	0	0.25	0.45
Nord (FR)	14	1	0.41	0.78
Nordrhein-Westfalen (DE)	7	0	0.17	0.42
Paris (FR)	8	1	0.33	0.62
Rhone (FR)	7	1	0.40	0.73
Seine Saint-Denis (FR)	10	0	0.41	0.64
Toscana (IT)	8	3	0.53	0.80
Yorkshire and the Humber (GB)	5	0	0.25	0.41
Zuid-Holland (NL)	8	0	0.29	0.51

Nevertheless, the correlations remained close or lower than 0.5 for 4 locations (Nordrhein-Westfalen, Yorkshire and the Humber, London and Zuid-Holland). The first two ones are coming from statistical uncertainty due to the low level of air pollution and of mortality, as considered in the previous analysis [26]. Taking in consideration these cases of low pollution levels is of importance to provide some control samples to be compared to higher pollution levels. The two other cases correspond to medium pollution levels, but compared to the other cities, PM levels remained relatively constant with time, with no well-defined periods of pollution peaks, as shown for Zuid-Holland (mainly Rotterdam city) in Figure 3.
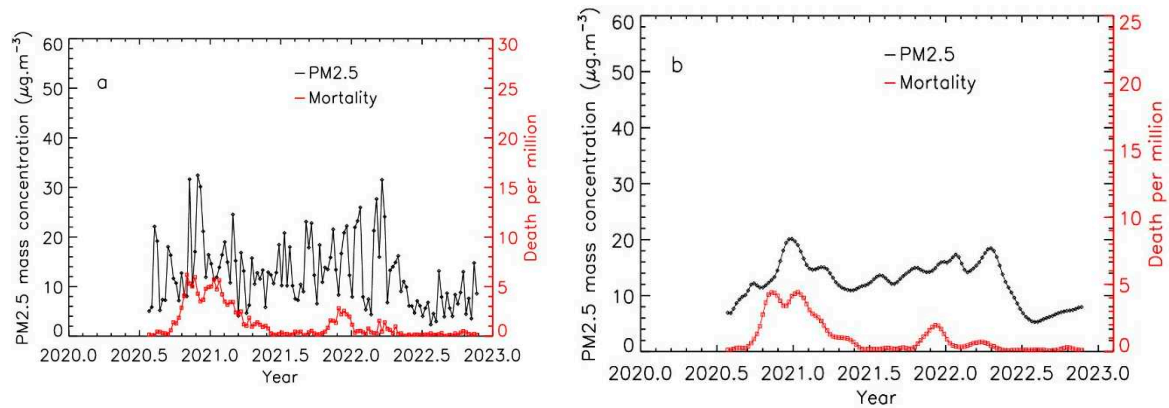

Figure 3. Time evolution of $PM_{2.5}$ levels and Covid-19 mortality for the Zuid-Holland region, exposed to low levels of pollution; a: weekly integrated data; b: weekly integrated data after applying the integration procedure for $PM_{2.5}$ data.

*3.2. Linear relation between $PM_{2.5}$ levels and Covid-19 mortality*

The relationship between Covid-19 mortality and $PM_{2.5}$ exposure was established by applying a linear fit for all locations. Individual measurements were scattered from one location to another, because of the possible heterogeneity of the population density (for example variations between large towns and rural zones), the health status of the populations that can influence the mortality and the local management of the pandemic [26].

Figure 4 presents the linear fits for the 16 location (mean correlation of 0.9 per fit). The same trend is systematically observed, an increase of mortality with increasing $PM_{2.5}$ level, even for locations with low air pollution levels. The difference of the slope and the value at origin ($PM_{2.5}$ value for zero-mortality) slightly differed from one location to another because of the population heterogeneity and pandemic management variations. The mean value of the slope was 0.39±0.22, meaning a mortality increase of about 40±20% per 1 $\mu g.m^{-3}$ $PM_{2.5}$ increase.

The shape of the curves for the time-evolution of $PM_{2.5}$ levels and Covid-19 mortality suggests that a relationship existed between the slope of the curves. The gradients values had similar magnitude for Covid-19 mortality and $PM_{2.5}$ spikes. Figures 5 and 6 present the examples of the Emilia Romagna and the Gironde regions. The mean features are well correlated between the two curves; nevertheless, the agreement between the two curves seems lower after 2022, which could be due to the effect of the vaccine that decreases the amplitude of the mortality, and to the progress of herd immunity.
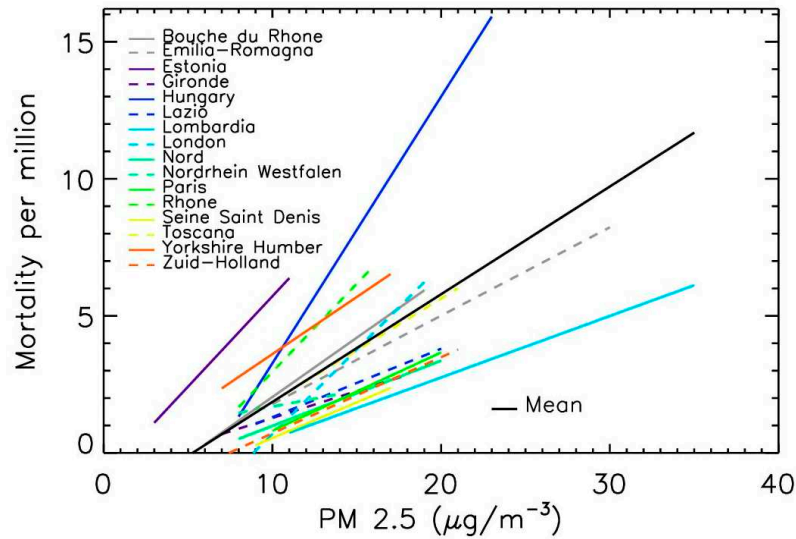
Figure 4. Trend evolution of Covid-19 mortality per million inhabitants vs. PM$_{2.5}$ for the 16 locations. The lines represent the linear fits in the domain range where PM$_{2.5}$ and mortality values are available.
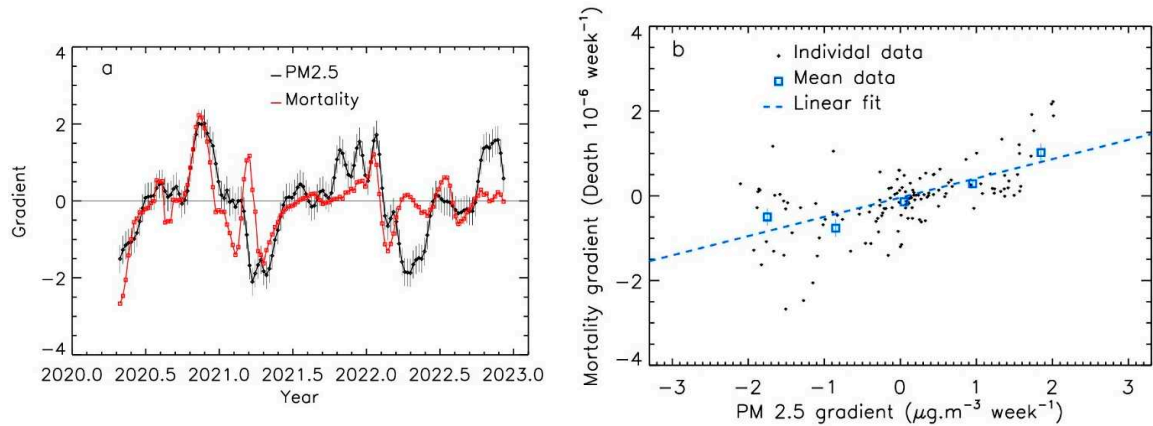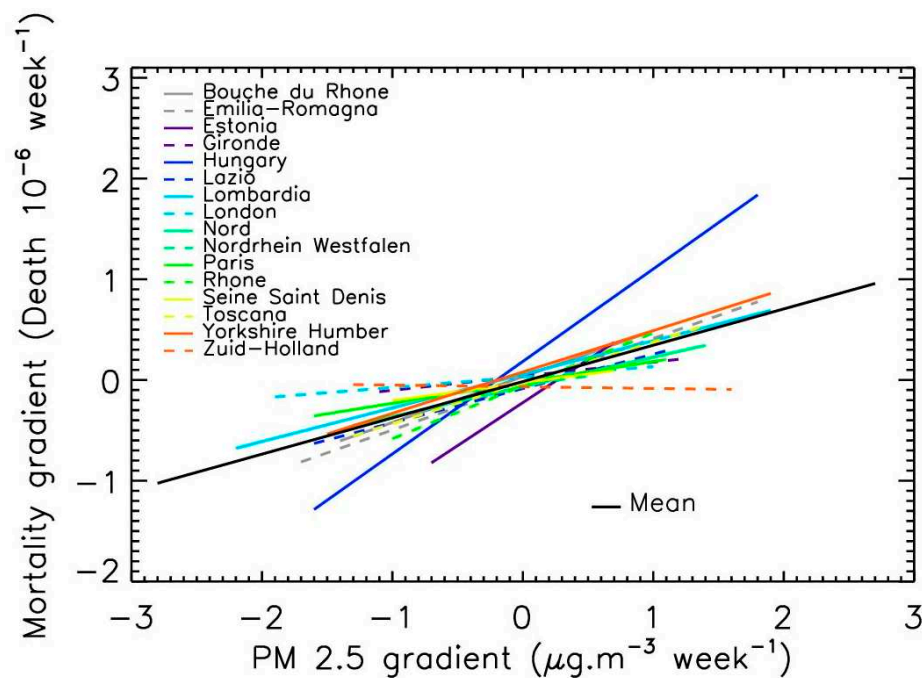

Figure 5. Gradient evolution of PM$_{2.5}$ levels and of Covid-19 mortality per million inhabitants, for the Emilia-Romagna region; a: time evolution; b: data and linear fit.
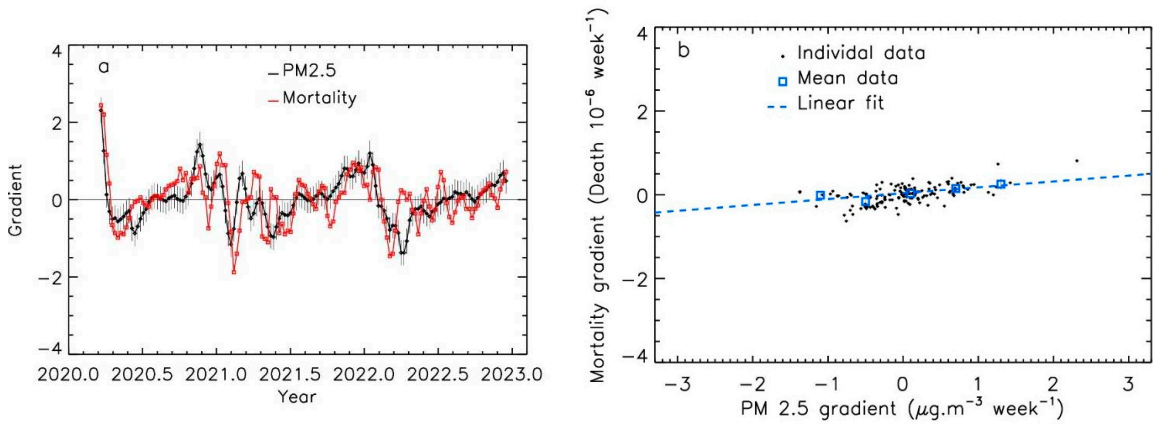
Figure 6. Gradient evolution of PM$_{2.5}$ levels and of Covid-19 mortality per million inhabitants, for the Gironde region; a: time evolution; b: data and linear fit.

The synthesis of the linear fits for the gradients at the 16 locations is presented in Figure 7 (mean correlation of 0.9 per fit). Globally, Covid-19 mortality gradients also linearly increased with increasing PM$_{2.5}$ gradients; the mean slope being 0.36±0.25. These results indicate that the strength of the PM$_{2.5}$ peak is also an increasing factor contributing to Covid-19 mortality.

In fact, 3 groups can be itemized: The locations presenting a strong slope (Hungary and Estonia), the locations with close-to-zero slope while having a medium mean level of pollution (Zuid-Holland, London), and the other cities. The difference between the first and the third group could once again be due to varying managements of the pandemic and population densities. Although only two cases have been spotted, the second group could indicate that cities with almost constant pollution levels, or without successive relatively short-lasting peaks of PM$_{2.5}$ and low values in-between, could limit the pulmonary inflammation. Thus, steep variations of PM$_{2.5}$ exposure rather than permanent exposure to medium pollution levels could be an aggravating factor of Covid-19 mortality.

Figure 7. Trend evolution of the gradients of Covid-19 mortality per million inhabitants vs. PM$_{2.5}$ levels, for the 16 locations. The lines represent the linear fits in the domain range where PM 2.5 gradients and mortality gradients are available.

4. Discussion

This study went more in depth on the investigation of the time-relation between PM$_{2.5}$ levels and Covid-19 mortality. Using data from 16 European representative locations, we found a Covid-19 mortality increase of about 40±20% per each 1 µg.m^{-3} PM$_{2.5}$ increase. This value is strongly higher than the 10% value previously reported [26,28–32] and can be explained by two different reasons. The first reason is that the mean value is dominated by the locations with high values as for Hungary, although most of the location remain in the 10-40% increase range. The second reason is that the method of data analysis we have proposed reduces the scatter of the data, increases the correlation between PM2.5 levels and Covid-19 mortality time-evolution, and thus increases the trend.

Furthermore, an exposure to several PM peaks during a 2-month period constituted the main factor for mortality increase, rather than a permanent exposition to (medium) pollution levels. The stronger the positive gradient of the pollution peak, the stronger the positive gradient of Covid-19 mortality; the effect is reversible, with a faster decrease of Covid-19 mortality being observed during faster decrease of PM$_{2.5}$ peaks. Thus, the lag-time combined with the strength and the duration of the pollution peaks should be considered by health policies for the management of the new and seasonal pandemics.

To explain the observed relation between $PM_{2.5}$ levels and Covid-19 mortality, it have proposed [18] that fine PM and overall ultra-fine-particles (UFP) increase the airway permeability by reducing tight junctions proteins, which facilitates virus penetration, as well as the fact that PM boosts the action of the angiotensin-converting enzyme 2 (ACE2). This explanation was confirmed in a review of the process of lung inflammation resulting from PM exposure and thus the impact on Covid-19 mortality following a cytokinic storm [37]. In particular, the authors studied the role of the angiotensin-converting enzyme 2 (ACE2), a receptor that is involved in the entry of the virus into pulmonary cells. Indeed, ACE-2 is a receptor for coronaviruses including the severe acute respiratory syndrome coronavirus 1 and 2 (SARS-CoV), and ACE-2 is overexpressed under chronic exposure to air pollution such as NO_2 and $PM_{2.5}$. ACE-2 is overexpressed in the case of medical comorbidities that contribute to the development of severe Covid-19.

Different natures of PM are present in ambient air [20]. Apart from dust episodes, in Europe mainly coming from Sahara [38], the main PM peaks are due to anthropogenic activities. The peaks occur during periods of anticyclonic conditions when pollutants accumulate and cannot be dispersed by winds [36,39]. The primary and secondary PM originate from vehicular traffic throughout the year (mainly carbonaceous particles), from industrials activities (all kinds of particles), from heating in winter (mainly carbonaceous particles), and from agricultural activities in autumn and spring (mainly ammonium). Other kinds of particles can be also present, like plastic, mineral and metal particles, coming from tyres, car and train brakes. In fact, no seasonal effect linked to the origin and thus the main nature of the particles was scrutinized during our analysis. The PM composition is complex; thus, it is difficult to estimate on which kind of particles the population was exposed. Consequently, we cannot conclude if Covid-19 mortality is due to all kinds of particles or to specific ones.

Another parameter to be considered is the size distribution of particles. We have used here the mass-concentration of $PM_{2.5}$, which corresponds to all particles smaller than 2.5 μm, although the largest ones mainly contribute to the values. Obviously, the smaller the particles, the deeper they penetrate in the human body. It has reported [4] that $PM_{0.1}$ (particles smaller than 100 nm) are those that cause more pulmonary inflammation. Thus, it should be better to consider the PM size-distribution rather than the integrated mass-concentrations, since the size-distribution depends on the origin of the pollution events [38]. The lower limit of scientific optical aerosol counters is of about 200nm (and of 300nm for Pollutrack sensors here used), thus they cannot detect such ultrafine particles. Expensive instruments could be used, using the Scanning Mobility Particle Sizer systems [40], but they are not operated in routine by air monitoring networks; they are mainly used during dedicated field campaigns. Thus, one solution for future works should be to use the smallest size classes of Pollutrack sensors in cities where they are already deployed (32 European capitals and major cities to date), to tentatively improve Covid-19 mortality analysis (or other respiratory illnesses) in function of the number concentrations of particles of a few hundred nm in size.

5. Conclusion

To better understand the relation between the time-evolution curves of $PM_{2.5}$ spikes and Covid-19 mortality, we have proposed to consider the historic population exposure to pollution peaks rather than instantaneous measurements, in 16 representative European cities. The related increase of Covid-19 mortality and $PM_{2.5}$ levels was linear both for increasing and decreasing periods. Probably due to vaccination campaigns and the collective immunity progression, the correlation decreased at the end of 2022 in Europe. As an example, in France, flu and bronchiolitis mortalities increased at the end of 2022 to the detriment of Covid-19 (although still present), occurring a few weeks after a strong $PM_{2.5}$ pollution peak.

The 2-month exposure period to $PM_{2.5}$ we have suggested is probably just a first step and should be adjusted through a more complex equation, for example by considering a decreasing memory effect on PM exposure with time. The first analysis presented here have shown the interest of considering $PM_{2.5}$ peaks for Covid-19 mortality rather than the permanent exposure to a mean level. It will be of interest to see if this approach is specific to this Coronavirus or could be also applied to

other respiratory diseases like the flu. Finally, other data than PM$_{2.5}$ mass-concentrations must be considered, in particular the number-concentration and size-distribution of particles smaller than 1 μm obtained with counters used during research campaigns and/or operated by private networks searching way beyond WHO recommendations.

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