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COVID19 outbreak in Lombardy, Italy: An analysis on the short-term relationship between air pollution, climatic factors and the susceptibility to SARS-CoV-2 infection

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ABSTRACT

Short-term exposure to air pollution, as well as to climate variables have been linked to a higher incidence of respiratory viral diseases. The study aims to assess the short-term influence of air pollution and climate on COVID19 incidence in Lombardy (Italy), during the early stage of the outbreak, before the implementation of the lockdown measures. The daily number of COVID19 cases in Lombardy from February 25th to March 10th’ 2020, and the daily average concentrations up to 15 days before the study period of particulate matter (PM_{10}, $PM_{2.5}$), O_3, $SO_{2,}$ and NO_2 together with climate variables (temperature, relative humidity – RH%, wind speed, precipitation), were analyzed. A univariable mixed model with a logarithm transformation as link function was applied for each day, from 15 days (lag15) to one day (lag1) before the day of detected cases, to evaluate the effect of each variable. Additionally, change points (Break Points-BP) in the relationship between incident cases and air pollution or climatic factors were estimated. The results did not show a univocal relationship between air quality or climate factors and COVID19 incidence. PM_{10}, $PM_{2.5}$ and O_3 concentrations in the last lags seem to be related to an increased COVID19 incidence, probably due to an increased susceptibility of the host. In addition, low temperature and low wind speed in some lags resulted associated with increased daily COVID19 incidence. The findings observed suggest that these factors, in particular conditions and lags, may increase individual susceptibility to the development of viral infections such as SARS-CoV-2.

1. Introduction

On the 20th of February, a man from the Lodi province (southern Lombardy) was the first known confirmed Italian case of infection by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In the following 20 days, cases in Lombardy rapidly rose, making the region the centre of the Italian Coronavirus Disease 2019 (COVID19) outbreak. At the same time, the uneven geographical distribution repeated itself also within Lombardy, with the disease clustering in the Provinces of Bergamo, Cremona and Lodi (Cereda et al., 2020).

SARS-CoV-2 infection spreads by human-to-human contact, mainly through respiratory droplets and the contact with contaminated surfaces, although airborne transmission is considered possible in closed environment spaces (Young et al., 2020). Areas with greater density population, therefore, could be at higher risk of contagion. Lombardy is characterized by very large urban areas, and ranks among the most polluted areas of Europe due to unfavorable geographical position, climate characteristic, land use, and emission sources (Carugno et al.,

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2018). Particularly, the Po river basin, which crosses the entire region, is characterized by a wind speed among the lowest in Europe, causing frequent phenomena of thermal inversion and trapping of smog and pollution close to the ground.

Previous studies showed that long- and short-term exposure to air pollution, including air particulate and gas pollutants, could be linked to a higher incidence of respiratory viral diseases (Carugno et al., 2018; Chen et al., 2010). While the presence of pathogenic viruses in the composition of particulate matter seems to be excluded, air pollution might promote airborne viral infections by other means, for instance affecting the host-immune system by reducing the airways macrophage response and boosting pro-inflammatory cytokines production (Becker and Soukup, 1999; Vandini et al., 2013). Additionally, respiratory viral infections could be influenced by the climate variables, such as temperature, humidity, precipitation, and wind speed, that appear to affect both virus infectivity and stability, and the host defenses, like mucociliary clearance (Sooryanarain and Elankumaran, 2015; Sundell et al., 2016).

The analysis of the influence of air quality and climate variables on the infection by SARS-CoV-2, however, showed controversial results in the previous studies, also for the presence both of methodological limitations and of several confounding factors (human interactions, lockdown measures, international travels, etc.) (Villenueve and Goldberg, 2020; Heederick et al., 2020; Riccò et al., 2020).

The aim of this retrospective population-based observational study is to assess the short-term relationship between air pollution or climatic factors and the COVID19 incidence in Lombardy, during the early stage of the outbreak.

2. Methods

2.1. Cases

The total daily numbers of new COVID19 confirmed cases for each province of Lombardy was retrieved from the website of the 'Dipartimento di Protezione Civile' (Italian civil defense body) (CPD, 2020). The examined period spanned from February 25th (the second day of social containment measures in Lombardy, including the suspension of public and didactic activities and social gatherings across the entire region, but no other restrictions of outdoor activities, except for few municipal areas, so-called "Red Zones", applying lockdown) to March 10th (24 h after the extension of the lockdown to the entire Country). This time span allowed to examine the spread of the virus right before the application of strict containment measures.

A confirmed case was defined as an individual with positive SARS-CoV-2 RT-PCR, targeting different viral genes (envelope protein - E, and RNA-dependent RNA polymerase- RdR), irrespective of clinical signs and symptoms (Cereda et al., 2020). In accordance with WHO suggestions, the diagnosis was simultaneously confirmed by at least two RT-PCR assays performed by two independent Regional Reference Laboratories.

In Lombardy, during the time study, every suspected case and the asymptomatic close contacts of confirmed cases were tested with a rhino-pharyngeal swab only on the February 25th, whereas starting February 26th testing was applied only to symptomatic suspected patients. The definitions of suspected case and close contact were based on the European Centre for Disease Prevention and Control (ECDC) guidelines (ECDC, 2020). In accordance with the regional and national regulations, the identification methods, case definition and testing strategy was not different throughout the Lombardy region.

2.2. Demographic indicators

The structural dependency index, the old-age dependency ratio and index, as retrieved from the Italian national institute for statistic (ISTAT), were analyzed for each Lombardy province (ISTAT, 2020). In addition, the average age, male-to-female ratio, and population density for each province was taken into account.

2.3. Air pollution and climatic factors

Air pollution and meteorological data from up to 15 days before the study period (February 10 - March 10) for each Lombardy province as collected by the monitoring stations of the Regional Environmental Protection Agency (ARPA) network were analyzed (ARPA, 2020).

Air pollution variables were: particulate matter with an aerodynamic diameter of less than 10 μm (PM_{10}) and 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3). PM_{10} and $PM_{2.5}$ were analyzed as daily mean concentration for each monitoring station. The measurements were performed using a chemical transport model (Silibello et al., 2008).

The climatic variables were analyzed as daily mean values of temperature (°C), percentage relative humidity (RH%), wind speed (Km/h), and precipitation (mm) as cumulative daily value for each monitoring station.

2.4. Statistical analysis

Air pollution and climatic data were summarized as mean and range by province. A 2-dimensional local kriging regression method was applied to the means of each single monitoring point to determine the province means. The kriging system was solved by finding the neighborhood of each grid point consisting of all environmental and climate monitors within the distance of 20 km.

The aim was to evaluate the relationship between air pollution and climatic factors detected in the days before and the spread of the COVID19 outbreak. For each single pollutant and climatic factor, a univariable hierarchical generalized mixed model with the number of new cases for each examined day for each province of Lombardy as dependent variable was run, assuming a Poisson distribution and using a logarithm transformation as link function. The province information was entered as random intercept. As independent factors in the univariable models, the daily mean levels of PM_{10}, $PM_{2.5}$, NO_2, SO_2, O_3, temperature, RH%, wind speed, and precipitation were considered. A model for each day before (lag) the day of the new cases was run to evaluate the effect of factors from 15 days (lag 15) to one day (lag 1) before the day of detected cases.

The above described demographic indicators were entered in the model for each province to account for potential confounders. All these indicators did not meet the criterion to enter the model ($p < 0.05$) and were removed.

The described approach has also been taken considering the aim of evaluating the epidemic in the region Lombardy as a whole, both to take into account the effects linked to regional mobility, considering that no restrictive measures to travel between municipalities had yet been applied during the study period, and to consider the phenomena of air pollutants dispersion, characteristic of the Po Valley.

For the first level unit (each day of data collection) $i = 1–16$ days from 25th February to 10th March, and for the second level unit (province) $j = 1$ to 12; the final model for the daily number of new cases y was:

$$y_{ij} = \beta_{0j} + \beta x_{ij} + \varepsilon_{ij} \quad (1)$$

where β_{0j} is the average intercept γ_{00}plus group-dependent deviation U_{0j}, β is the regression coefficient for the air pollution and climate factors, and εij is the residual term.

In the second set of analyses, we evaluated possible change points (or Break Points; BP) in the relationship between incident cases and the independent factors. So we classified those factors and applied the model [1]; the solutions for factor class effect were used as the dependent variables to estimate BP in the relationship between incident cases and air pollution or climatic factors. These BP would then determine the risk threshold(s) in these populations. The following model was used:

$$y_i = x_i^T \beta + u_i \quad (i = 1, \ldots, n) \tag{2}$$

where at time i, y_i is an observation of the dependent variable (e.g., least squared means of incident cases), x_i^T is a $k \times 1$ vector of regressors, with the first component usually equal to unity; β is the k × 1 vector of regression coefficients, which may vary over time (air pollution or climatic factor class); u_i are iid(0,σ^2) (i.e., u_i is a $k \times 1$ vector of residuals, which are independent and identically distributed with mean 0 and standard deviation σ^2).

In this second phase, we tested the null hypothesis that the regression coefficients remain constant (reduced model) compared with the alternative hypothesis that at least 1 coefficient varies over time (complete model). If the increase in the sum of square errors from the complete to the reduced model is significantly large, then the null hypothesis can be rejected, concluding that the complete model works well and a significant break point does exist (i.e., a significant change in incident cases due to the independent variables has been detected). The analyses were repeated by regressing the least squares means on the independent variable class for each of the 15 days before the test-day record.

A two tail p-values<0.05 was used to assess statistical significance. The krige2d and glimmix models in the first step of analysis were performed in SAS 9.4 (SAS Institute, Cary NC). The R software and the "struck change" package were used in the second set of analyses (R Core Team, 2019; Zeileis et al., 2002).

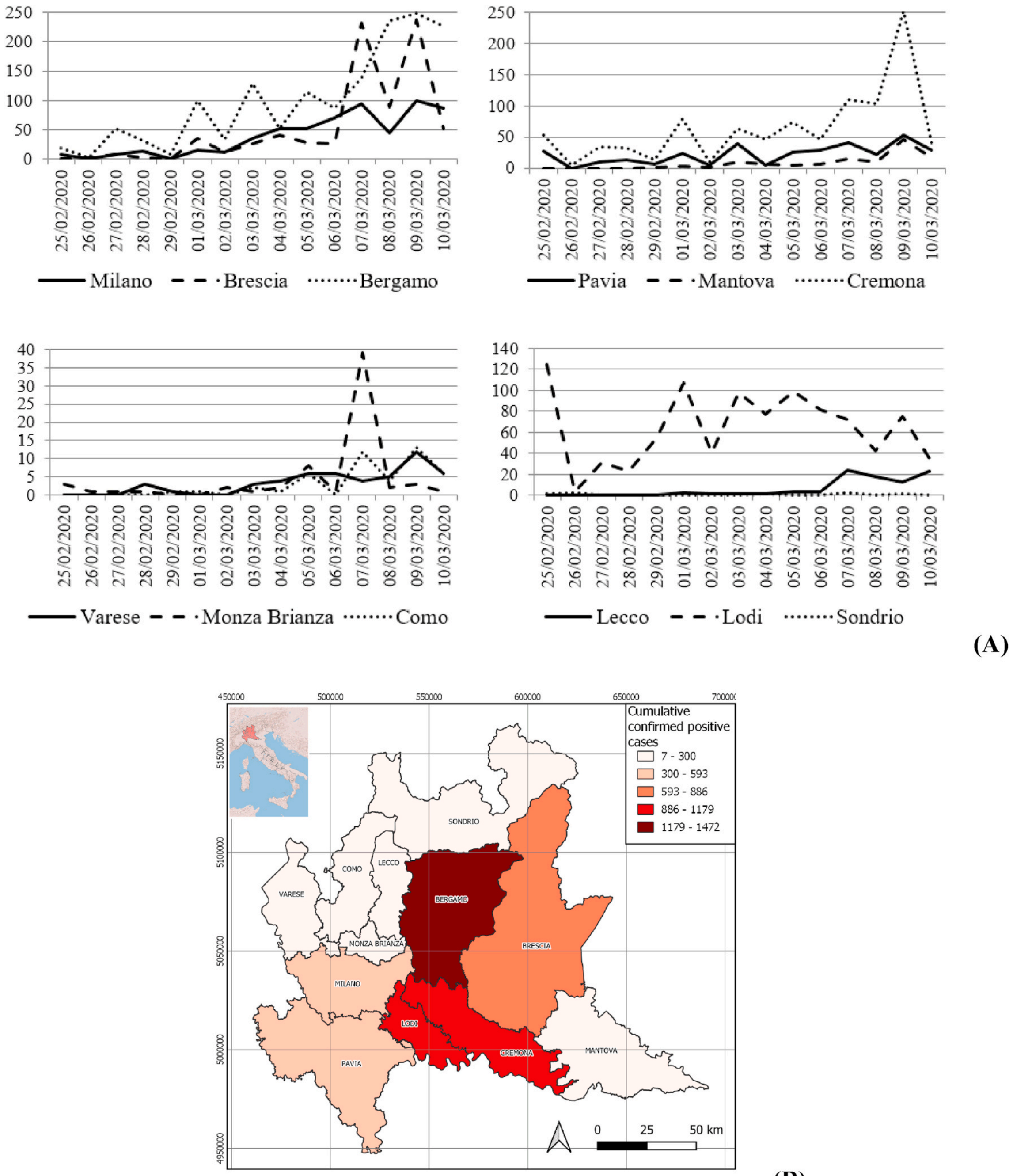

Fig. 1. Number of new daily confirmed cases by province grouped by population density (A) and of cumulative confirmed cases by province (B) in the study period.

3. Results

The temporal trend of the COVID19 outbreak in Lombardy within the examined period is detailed in Fig. 1, and the levels of air pollution and climatic factors up to 15 days before the study period are reported in Table 1.

COVID19 spread in Lombardy as follows (cumulative cases in brackets): by March the 10th the province of Bergamo was the most affected (1472), followed by Lodi (963), Cremona (957), Brescia (790) and Milan (592). Of note, in March there was a spread of incidence in Bergamo, Brescia and Cremona with an average of 136, 77 and 82 new daily cases respectively. The trend in the Lodi province, where the outbreak started, was slightly different with an average of 72 new daily cases, but with a flatter distribution from February to March.

The regression coefficients of model [1] by lags 1–15 for each independent factor are reported in Table 2. The effect of PM_{10} until lag12 was to reduce significantly the number of cases, while from lag 13 to 15, the coefficients became positive and significant ($p < 0.001$), with the highest value at lag13 ($b = 0.014$). The effect of $PM_{2.5}$ was similar as compared to PM_{10}, with significant ($p < 0.001$) coefficients: negative from lag1 to lag12, and positive at lag13 and lag14, while at lag15 the coefficient value, even statistically significant, resulted not estimated.

The NO_2 coefficients did show a univocal trend through the lags, with all coefficients resulted significant ($p < 0.001$) and negative, the higher at lag11 ($b = -0.053$), lag13 ($b = -0.028$) and lag14 ($b = -0.032$). A significant inverse relation was also observed for SO_2 levels from lag6 to lag15, with the exception of lag9, while small significant ($p < 0.001$) positive coefficients, suggesting a slight effect to increase the number of cases, were observed at lag1 ($b = 0.001$) and lag5 ($b = 0.001$). Regarding the O_3 concentrations, significant ($p < 0.001$) negative coefficients resulted at lag3 ($b = -0.008$) and lag5 ($b = -0.007$), whereas coefficients resulted significant ($p < 0.001$) and positive at lag1 and from lag6 to lag14, with higher effect at lag10 ($b = 0.043$), lag11 ($b = 0.031$) and lag12 ($b = 0.038$).

Temperature showed a significant ($p < 0.001$) inverse relation to the number of cases from lag1 to lag11, with higher values at lag3 ($b = -0.262$) and lag5 ($b = -0.261$); from lag12 to lag15 coefficients resulted significant ($p < 0.001$) and positive, the higher at lag13 ($b = 0.25$) and lag14 ($b = 0.227$). RH% showed significant ($p < 0.001$) coefficients, positive from lag1 to lag7, and negative from lag9 to lag12. For wind speed the coefficients were significantly ($p < 0.001$) negative from lag1 to lag3 and at lag14 and lag15, but at lag4 and from lag6 to lag13 the relation became direct and significant ($p < 0.001$), the higher coefficients at lag10 ($b = 0.359$) and lag12 ($b = 0.357$). Precipitations were very low in the period analyzed; however, significant ($p < 0.001$) coefficients were observed, positive from lag1 to lag9, and negative from lag10 to lag15, with maximum effect at lag14 ($b = -0.568$).

The analysis of structural changes (STRUCH, model [2]), estimated at each lags (Table 3), showed a BP of the STRUCH for PM_{10} at 30 $\mu g/m^3$ at lags 3 and 11, at 40 $\mu g/m^3$ at lags 5, 6, 7, 8, at 50 $\mu g/m^3$ at lag10, but the increase above these threshold values was always related to a decreasing of cases. Similarly, $PM_{2.5}$ levels above the threshold values between 24 $\mu g/m^3$ and 34 $\mu g/m^3$ determined a decreasing trend in the number of new cases at lags from 1 to 8, while levels above 29 $\mu g/m^3$ determined an increase of cases at lags 14 and 15 (Fig. 2). NO_2 levels above 24 $\mu g/m^3$ at lags 7 and 12 and above 29 $\mu g/m^3$ at lag11 determined a decreasing of the new cases, while an increasing change in the trend of cases occurred in almost all lags for SO_2 levels above the thresholds 2 $\mu g/m^3$ or 3 $\mu g/m^3$. The relationship between O_3 and the number of cases intensified for levels above 44 $\mu g/m^3$ at lag10 (Fig. 2).

BPs were found for temperature below 5 °C at lags 1, 4, 7, 8, 9 and 10, and for temperature below 6 °C at lags 3 and 5 (Fig. 2), in all the cases with the trend of cases increasing. Significant BPs in the relationship between RH% and number of cases were observed, however changing between the lags: above 79% for lags 5 and 7 the cases increase, while above 49% for lags 10 and 11 the cases decrease. The analysis of STRUCH for wind speed allowed to find as BP the value of 2.5 m/s at lags 14 and 15 (Fig. 2), showing a decrease of the occurrence of new cases when this BP was exceeded.

4. Discussion

In the present study, a clear short-term relationship between air quality or climate factors and COVID19 incidence in the early phase of Lombardy outbreak was not observed, although a possible association was found in some specific lags for PM_{10}, $PM_{2.5}$, O_3 concentrations, temperature, and wind speed levels.

The outbreak of COVID19 in Italy has immediately showed strong regional differences, with most cases concentrated in Lombardy (Remuzzi and Remuzzi, 2020). Our study, however, was particularly

Table 1

Average (Range) of each air and climate factor by province in the period up to 15 days before the study period considered for case identification.

	PM_{10} ($\mu g/m^3$)	$PM_{2.5}$ ($\mu g/m^3$)	NO_2 ($\mu g/m^3$)	SO_2 ($\mu g/m^3$)	Ozone ($\mu g/m^3$)	Temperature (°C)	RH%	Wind velocity (m/sec)	Precipitation (mm/h)
Milano	41.3 (13.4–92.4)	33.5 (8.0–77.7)	47.9 (26.8–80.9)	3.8 (2.8–4.9)	22.3 (4.9–55.2)	7.9 (4.0–12.2)	73.3 (30.5–97.9)	1.4 (0.8–3.8)	0.0 (0.0–46.1)
Brescia	41.3 (13.3–79.3)	30.6 (10.0–65.0)	38.2 (21.0–59.3)	1.0 (0.1–2.7)	26.4 (3.2–57.8)	6.0 (3.1–9.4)	62.5 (31.1–94.9)	2.0 (1.1–4.2)	0.1 (0.0–24.9)
Bergamo	36.6 (9.8–82.4)	31.3 (7.4–66.6)	38.0 (16.8–60.9)	2.7 (1.2–4.4)	29.2 (7.1–65.6)	5.2 (2.4–9.5)	63.5 (30.2–94.5)	1.6 (0.9–3.9)	0.1 (0.0–36.5)
Pavia	36.6 (11.4–90.6)	32.8 (7.3–77.0)	35.3 (19.4–64.2)	4.4 (3.4–6.7)	22.2 (2.7–56.8)	6.9 (3.3–12.6)	75.1 (35.6–97.9)	1.7 (0.8–4.2)	0.0 (0.0–28.3)
Mantova	43.1 (8.1–89.0)	33.0 (2.3–72.3)	30.1 (14.3–50.1)	2.2 (1.6–4.0)	25.3 (2.8–54.8)	7.1 (2.9–10.0)	85.1 (37.1–99.6)	1.5 (0.8–4.1)	0.0 (0.0–13.2)
Cremona	44.0 (15.2–85.0)	41.0 (12.3–84.5)	34.3 (18.2–57.5)	1.6 (0.8–3.6)	20.9 (1.4–73.6)	6.6 (2.7–10.4)	85.9 (36.1–99.6)	1.3 (0.6–4.4)	0.0 (0.0–13.0)
Varese	29.3 (7.3–77.0)	23.0 (6.0–64.5)	38.4 (21.0–63.7)	3.6 (2.6–8.4)	29 (4.9–62.4)	6.2 (2.7–11.1)	63.8 (33.8–96.9)	1.7 (0.8–5.0)	0.0 (0.0–47.3)
Monza Brianza	(–)	37.0 (5.0–74.0)	48.6 (20.2–82.1)	5.4 (3.7–9.2)	25.5 (7.5–63.1)	6.8 (2.8–10.7)	(–)	(–)	0.0 (0.0–51.0)
Como	29.0 (5.0–77.7)	28.0 (4.0–41.8)	37.9 (18.5–67.5)	1.5 (0.7–3.4)	31.0 (6.5–72.4)	6.0 (3.1–11.1)	57.4 (24.7–92.0)	2.5 (1.3–6.3)	0.0 (0.0–42.2)
Lecco	25.0 (6.2–63)	18.0 (2.7–50.3)	32.5 (10.7–50.2)	1.6 (0.7–3.0)	45.5 (20.0–77.2)	5.8 (2.9–10.9)	63.0 (28.2–94.1)	1.3 (0.6–4.1)	0.0 (0.0–45.0)
Lodi	40.0 (10.7–89.4)	27.0 (4.0–67.5)	35.9 (15.1–53.2)	2.3 (1.3–3.6)	22.6 (2.8–58.4)	6.8 (3.2–11.4)	88.7 (43.4–99.7)	1.7 (0.9–5.6)	0.0 (0.0–19.0)
Sondrio	22.3 (6.5–52.5)	17.5 (4.0–33)	24.7 (10.6–39.6)	2.3 (1.3–4.7)	38.3 (16.0–66.1)	3.7 (1.6–8.2)	57.5 (37.8–92.1)	2.1 (0.8–6.5)	0.1 (0.0–19.3)

Table 2

Regression coefficients (standard error) by lags of each air pollution and climatic factor.

	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)	NO_2 (μg/m^3)	SO_2 (μg/m^3)	Ozone (μg/m^3)	Temperature (°C)	RH%	Wind velocity (m/sec)	Precipitation (mm/h)
Lag1	−0.017	−0.003	−0.004	0.001	0.006	−0.093	0.003	−0.061	0.005
	(0.0004)	(0.001)	(0.001)	(0.0001)	(0.002)	(0.0002)	(0.008)	(0.001)	(0.013)
Lag2	−0.015	−0.002	−0.006	0.0003	0.002	−0.128	0.008	−0.051	0.009
	(0.0004)	(0.001)	(0.001)	(0.0001)$^{\#}$	(0.002)$^{\#}$	(0.0001)	(0.008)	(0.001)	(0.012)
Lag3	−0.020	−0.003	−0.009	0.0001	−0.008	−0.262	0.01	−0.054	0.017
	(0.0004)	(0.001)	(0.001)	(0.0001)$^{\#}$	(0.001)	(0.0001)	(0.009)	(0.001)	(0.013)
Lag4	−0.025	−0.004	−0.007	0.0004	0.001	−0.248	0.013	0.126	0.023
	(0.0004)	(0.001)	(0.001)	(0.0001)$^{\#}$	(0.001)$^{\#}$	(0.0002)	(0.009)	(0.001)	(0.015)
Lag5	−0.022	−0.004	−0.009	0.001	−0.007	−0.261	0.014	0.008	0.031
	(0.0004)	(0.001)	(0.001)	(0.0002)	(0.001)	(0.0002)	(0.009)	(0.001)$^{\#}$	(0.014)
Lag6	−0.025	−0.005	−0.008	−0.002	0.004	−0.169	0.017	0.215	0.029
	(0.0004)	(0.001)	(0.001)	(0.0002)	(0.001)	(0.0001)	(0.009)	(0.001)	(0.015)
Lag7	−0.018	−0.003	−0.009	−0.0004	0.004	−0.227	0.014	0.15	0.037
	(0.0004)	(0.001)	(0.001)	(0.0002)	(0.001)	(0.0001)	(0.009)	(0.001)	(0.015)
Lag8	−0.025	−0.03	−0.01	−0.002	0.03	−0.14	0.001	0.08	0.024
	(0.0004)	(0.001)	(0.001)	(0.001)	(0.001)	(0.0001)	(0.008)#	(0.001)	(0.015)
Lag9	−0.020	−0.026	−0.004	0.00004	0.029	−0.195	−0.015	0.102	0.054
	(0.001)	(0.001)	(0.001)	(0.001)$^{\#}$	(0.009)	(0.0001)	(0.009)	(0.001)	(0.015)
Lag10	−0.025	−0.029	−0.06	−0.872	0.043	−0.07	−0.029	0.359	−0.161
	(0.002)	(0.001)	(0.001)	(0.001)	(0.029)	(0.038)	(0.009)	(0.001)	(0.013)
Lag11	−0.015	−0.019	−0.053	−0.72	0.031	−0.057	−0.017	0.267	−0.442
	(0.002)	(0.001)	(0.001)	(0.001)	(0.049)	(0.037)	(0.009)	(0.001)	(0.014)
Lag12	−0.009	−0.013	−0.06	−0.607	0.038	0.122	−0.012	0.357	−0.515
	(0.002)	(0.001)	(0.001)	(0.001)	(0.045)	(0.038)	(0.008)	(0.001)	(0.013)
Lag13	0.014	0.013	−0.028	−0.629	0.007	0.25	0.017	0.033	−0.181
	(0.002)	(0.001)	(0.001)	(0.001)	(0.028)	(0.036)	(0.008)	(0.001)$^{\#}$	(0.016)
Lag14	0.013	0.012	−0.032	−0.25	0.013	0.227	0.017	−0.096	−0.568
	(0.002)	(0.001)	(0.001)	(0.001)	(0.048)	(0.036)	(0.008)	(0.001)	(0.022)
Lag15	0.012	0	−0.009	−0.495	0.002	0.101	0.01	−0.235	−0.092
	(0.002)	(0.001)	(0.001)	(0)	(0.024)$^{\#}$	(0.037)	(0.009)	(0.001)	(0.024)

All parameters resulted statistically significant ($p < 0.001$), except those indicated with $^{\#}$.

focused only on the very early stage of the Lombardy outbreak, because it represented a unique peculiar situation for analyzing the relationship between COVID19 and air pollution. In fact, Lombardy was characterized during the study period by the absence of stay-at-home policy, with minimal containment measures, limited to the closure of schools and the prohibition of social gatherings. Furtherly, case definition, testing strategy and restrictions measures were absolutely homogeneous throughout the region, except for very few small lockdown areas in the province of Lodi. Moreover, Lombardy is a very polluted area characterized by long range transport of pollutants, so that almost all the region suffers of very similar conditions (Caserini et al., 2017).

Another peculiar characteristic of the study period in Lombardy was that no testing difficulties were reported. Lombardy's strong hospital system, coupled with a poor decentralisation of medical resources in the territory, in fact, created a situation of a predominantly hospital-based management and testing of the symptomatic suspected cases, differently from other countries and pandemic stages. Delay in the notification system, however, occurred only in a later phase than our study period, according to the increased number of cases and to the indication of home health care of the not severe cases. Finally, in the study period, almost only symptomatic suspected cases were tested. This limitation of the study, however, allowed anyway to investigate the effect of air pollution on the susceptibility to the infection by SARS-CoV-2.

The regression analysis showed a similar pattern for PM_{10} and $PM_{2.5}$, with a significant association with the daily number of cases, negative in the lags closest to the date of cases diagnosis, and positive in the last lags. The negative coefficients were related to the contemporary progressive decrease in PM_{10} and $PM_{2.5}$ levels, due to the application of partial containment measures (data not showed), and increase of the number of confirmed cases. Lags 13–15, on the contrary, are related to the period 10–25 February, characterized by the complete lack of containment measures and a possible association with the COVID19 incidence was observed.

Previous studies on the relationship between PM_{10} and daily COVID19 incidence showed not univocal results (Jiang et al., 2020; Zhu et al., 2020). Although some Authors have hypothesized that particulate matter might provide condensation nuclei for viral attachment, the possibility that PM_{10} can facilitate the infection carrying the SARS CoV-2 seems to be unlikely, also because only particles with diameter lower than 5 μm can reach the type II alveolar target cells highly expressing the angiotensin-converting enzyme 2 (ACE2), binding receptor for the virus (Lan et al., 2020; Zoran et al., 2020). Moreover, it appears unlikely that the virus can maintain structure and function even after a prolonged exposition to outdoor temperature and UV radiation (Cao et al., 2014). On the other hand, the positive association between PM_{10} and daily COVID19 cases in lags far from the occurrence of cases could be due to the widely recognized effects of PM_{10} on the host inflammatory response, leading to an over-expression of inflammatory cytokines, as IL-6, IL-8 and TNF-α, and chemokines in alveolar macrophages with the consequence to impair the first line of defense (Carugno et al., 2018; Ishii et al., 2004). Moreover, PM_{10} might as well downregulate the innate immune responses and upregulate several metabolic pathways-related genes in the initial phase of the disease, i.e. before the emergence of symptoms, thus promoting the viral replication of RNA viruses, as previously observed for New-Castle Disease virus (NDV) and influenza viruses (Mishra et al., 2020).

Positive coefficients in the last lags agree with the influence of daily levels of $PM_{2.5}$ on COVID19 outbreak reported in previous studies, and are probably related both to the effect of bronchial immunity impairment and damage to the epithelial integrity, and to a reduction in lung function and induction of respiratory symptoms (Ciencewicki and Jaspers, 2020; Jiang et al., 2020; Seposo et al., 2020; Zhu et al., 2020; Zoran et al., 2020).

It is possible to hypothesize, therefore, that exposure to elevated levels of PM_{10} and $PM_{2.5}$ could favor the onset of symptoms or more severe clinical pictures of COVID19, resulting in a higher rate of confirmed cases, also according to the fact that almost exclusively symptomatic cases were included in our study.

Table 3
Results of the Structural change and maximum breakpoint analysis by lags for each air and climate factors.

Parameter	Lag1	Lag2	Lag3	Lag4	Lag5	Lag6	Lag7	Lag8	Lag9	Lag10	Lag11	Lag12	Lag13	Lag14	Lag15
PM_{10} (μg/m^3)	–	20–30	20–30	–	30–40	30–40	30–40	30–40	20–30	40–50	20–30	20–30	–	–	30–40
B	–	−7.724	−9.205*	–	−9.08*	−11,394§	−10.275*	−12.514§	−33.156	−12.867*	−17.452*	−8.43	–	–	8.122
R^2	–	0.440	0.620	–	0.566	0.883	0.596	0.901	0.354	0.549	0.536	0.322	–	–	0.437
$PM_{2.5}$ (μg/m^3)	25–29	30–34	25–29	20–24	25–29	20–24	25–29	25–29	–	–	–	–	–	35–39	25–29
B	−8.807ˆ	−9.564*	−10.714§	−11.277§	−10.616ˆ	−10.358ˆ	−8.779ˆ	−12.843§	–	–	–	–	–	9.093ˆ	11.053ˆ
R^2	0.615	0.493	0.852	0.765	0.739	0.611	0.655	0.895	–	–	–	–	–	0.264	0.661
NO_2 (μg/m^3)	20–24	–	–	–	30-34.	–	20–24	20–24	20–24	–	25–29	20–24	–	–	–
B	2.355	–	–	–	−5.276	–	−11.477*	−68.264	−13.184	–	−14.082ˆ	−15.681*	–	–	–
R^2	0.069	–	–	–	0.322	–	0.509	0.346	0.443	–	0.868	0.586	–	–	–
SO_2 (μg/m^3)	2.5–3.0	4–4.5	–	1.5–2.0	2–2.5	2.5–3.0	2–2.5	1.5–2.0	2–2.5	1.5–2.0	1.5–2.0	1.5–2.0	1.5–2.0	3.5–4.0	1.5–2.0
B	−16.282ˆ	−0.662	–	−23.863§	−20.355§	−22.142ˆ	−18.871§	−30.509ˆ	−21.209ˆ	−50.681ˆ	−33.977ˆ	−25.013*	−12.421*	3.993	−9.306
R^2	0.634	0.002	–	0.802	0.757	0.688	0.847	0.682	0.663	0.609	0.607	0.369	0.387	0.224	0.167
Ozone (μg/m^3)	–	30–34	35–39	–	25–29	–	–	–	–	40–44	–	40–44	40–44	40–44	40–44
B	–	0.447	−6.055*	–	−2.731	–	–	–	–	14.852*	–	28.166	−2.84	−1.21	0.629
R^2	–	0.003	0.447	–	0.072	–	–	–	–	0.522	–	0.403	0.065	0.008	0.002
Temperature (°C)	4–5	7–8	5–6	4–5	5–6	5–6	4–5	4–5	4–5	4–5	5–6	4–5	–	–	7–8
B	−8.839*	−6.728	−19.267ˆ	−26.004*	−17.477*	−16.824	−23.946ˆ	−18.994§	−21.494§	−19.672ˆ	−6.879	0.164	–	–	6.6
R^2	0.599	0.3	0.71	0.769	0.541	0.431	0.708	0.839	0.875	0.671	0.167	0	–	–	0.431
RH %	45–49	55–59	–	–	75–79	–	75–79	45–49	45–49	45–49	45–49	50–54	65–69	65–69	60–64
B	−6.705	−4.227	–	–	11.259*	–	10.604*	−3.756	−7.214	−16.837*	−14.101ˆ	0.422	1.667	5.07	−2.245
R^2	0.049	0.132	–	–	0.446	–	0.494	0.051	0.163	0.431	0.529	0.002	0.027	0.106	0.031
Wind velocity (m/sec)	1.5–2	1–1.5	1.5–2	2–2.5	–	2.5–3	2–2.5	–	2.5–3	2–2.5	–	2.5–3	–	2–2.5	2–2.5
B	−1.269	1.608	−1.922	4.744	–	4.713	6.278*	–	−1.892	18.146ˆ	–	27.261§	–	−9.78*	−11.173*
R^2	0.014	0.043	0.046	0.219	–	0.147	0.456	–	0.039	0.744	–	0.933	–	0.489	0.564

*$p < 0.05$; ˆ$p < 0.01$; §$p < 0.001$.

In contrast to the previous evidence that air levels of NO_2 influenced the diffusion and the daily spread of respiratory viruses and to the findings of recent studies on COVID19, a negative relationship between NO_2 and COVID19 cases was found in our study (Carugno et al., 2018; Zhu et al., 2020). These findings could be explained by the progressive decrease of NO_2 as a consequence of the first containment strategies adopted in Lombardy, while the disease was rapidly spreading. Similarly, a decrease of SO_2 concentrations in Lombardy because of the lockdown measures could explain the inverse relation between SO_2 and the occurrence of cases for almost all the lags investigated (Mahato et al., 2020). However, a negative relationship between SO_2 concentrations and COVID19 confirmed cases was also previously observed, suggesting a possible anti-viral property of SO_2 to be further investigated (Zhu et al., 2020).

Although the progressive increase of O_3, possibly resulting from the first containment measures, could have contributed to the observed positive relationship between O_3 levels and COVID19 new daily cases, the findings seem to agree with previous evidence that O_3 exposure facilitate viral infections (Becker et al., 1998). Indeed, O_3 exposure, could induce oxidative stress causing airways inflammation and increased respiratory morbidities, and inversely modify the expression levels of human airways proteases, disrupting the protease/antiprotease balance in the airway fluids (Kesic et al., 2012). Our findings, however, are related to the average daily O_3 concentration, used to better evaluate the effects of the overall 24 h' exposure, considering that O_3 production can be delayed and happens also far from the release of its precursors, undergoing to considerable transport phenomena (Zoran et al., 2020). Moreover, daily O_3 exposure has been associated to an increased prevalence in COVID19 cases (Zhu et al., 2020).

In the evaluation of the impact of climatic variable, the evidence that outdoor transmission seems to be very low in causing the COVID19 outbreak, should be considered. In our analysis, a negative relationship between outdoor temperature and the COVID19 spread in Lombardy was observed for the lags from 1 to 11, according with previous evidence on SARS-CoV-2, as well as other respiratory virus infection (Casanova et al., 2010; Jiang et al., 2020; Wang et al., 2020; Wu et al., 2020). Moreover, phagocytic function of alveolar macrophages declines under cold stress in vitro experiment, and breathing cold air can lead to bronchial constriction, which may promote susceptibility and accelerate the spread of viral pulmonary infections (Luo et al., 2017; Kudo et al., 2019).

No clear relationship between RH% and confirmed COVID19 daily new cases was described, according to the not univocal results reported in the previous studies (Adhikari and Yin, 2020; Jiang et al., 2020; Luo et al., 2020). Precipitations also showed a not univocal trend, probably, due to the very low daily average precipitation level in the analyzed period in Lombardy, although the negative association showed from lag10 to lag15 could be linked to a decreased washout of pollutants. Finally, a not-univocal relationship between wind speed and the new daily cases was observed, with large variation across the lags, although a BP at the value of 2.5 m/s, only at lags 14 and 15, was found. These findings suggest that higher wind speed could reduce the occurrence of new cases, probably by favoring the dispersion of PM_{10} and $PM_{2.5}$, that our study showed to influence COVID19 cases only in the same lags (Zoran et al., 2020).

Our study has its main strength in the analysis of the short-term relationship between the daily levels of several pollutants and meteorological parameters and the daily incidence of COVID19, specifically during the early stage of the outbreak in a restricted region severely affected by the pandemic, before the implementation of strict containment policies and testing strategy that can distort associations between air pollution and COVID19. In fact, to avoid the changes in transmissibility and contact rates occurring over time as a result of implementation of control measures, the study period has been focused on the days between the first COVID19 case and the issuance of lockdown measures. Moreover, the time series study design approach allowed to

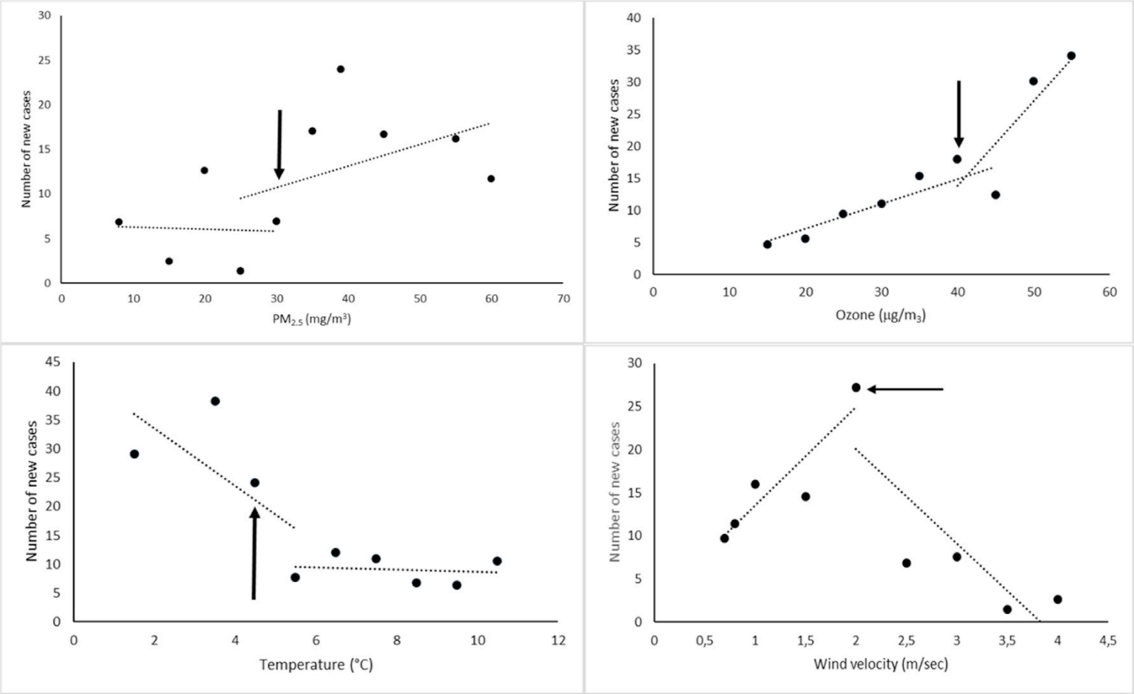

Fig. 2. Structural change analysis for $PM_{2.5}$ at lag15, ozone at lag10, temperature at lag10, wind velocity at lag15.

estimate short-term health effects associated with exposures, avoiding the ecological design that suffers from severe biases.

This study, however, has several limitations, similar to the previous literature on the topic (Ciencewicki et al., 2007; Villenueve and Goldberg, 2020; Heederik et al., 2020). First, the testing strategy adopted in Lombardy during the outbreak caused under-reporting of cases, particularly for the presence of asymptomatic and mild-symptomatic subjects. In the study period, almost only symptomatic subjects were tested, so that the influence of air pollution should be interpreted only considering the effect on the onset of symptomatic COVID19 cases. In this view, all the results can be evaluated only according to the hypothesis of the influence of air pollution on the host susceptibility. Second, the link among the different COVID19 cases has not been possible to analyze due to the design of the study. Moreover, potential factors such as population movement or daily commuting between the provinces, that could have influenced both the transmission and the recording of the data, were not considered in the study. A further intrinsic limitation of the design of the study is the possible errors due to the difference between the day of the onset of symptoms and the day of testing or notification. Finally, data collected by stationary monitors, represent only an estimation of individual exposure and a sampling system with limited spatial resolution, as well as individual risk factors (occupation, race, socioeconomic status, underlying health conditions) were not taken in consideration too.

In conclusion, the observed findings showed a not univocal relationship between air pollution or climatic factors and the incidence of COVID19 cases, reflecting the complexity of this phenomenon that is conditioned by many different factors (Riccò et al., 2020). However, although air pollution and climate do not seem to be a cause of SARS-CoV-2 spread, also considering the main influence of person-to-person contact as way of transmission and the fact that most of the contagions takes place in indoor environment, the short-term exposure to PM_{10}, $PM_{2.5}$ and O_3 in some lags seems to be related to an increased incidence of COVID-19 infection, probably linked to an increased susceptibility of the host due to the dysregulation of the immune system or the worsening of conditions associated with severe SARS-CoV-2 infection. In addition, low temperature and low wind speed in some lags resulted associated with increased daily COVID19 incidence. Considering the several limitations of the study, the observed findings have to be considered a step for future research on this topic.

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Credit author statement

AS, SL, LS, GD and PL conceived the study. AS, GL and HJ searched the literature. AS, SL, AM and MM collected the data and prepared the database. Data analysis has been carried out and interpreted by NB and PT. The thematic map has been carried out by AM. AS, SL, NB, HJ, GL and PT contributed to initial drafting of the manuscript. All the authors contributed to interpretation of data and critical revision of the report. PT, GD, LS, MM and PL verified the data and contributed to study supervision. All the Authors have actively participated to the preparation of the final proof of the manuscript.

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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