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Research article

Early-phase pandemic in Italy: Covid-19 spread determinant factors

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ABSTRACT

Although the Covid-19 pandemic is still ongoing, the environmental factors beyond virus transmission are only partially known. This statistical study has the aim to identify the key factors that have affected the virus spread during the early phase of pandemic in Italy, among a wide set of potential determinants concerning demographics, environmental pollution and climate. Because of its heterogeneity in pollution levels and climate conditions, Italy provides an ideal scenario for an ecological study. Moreover, the selected period excludes important confounding factors, as different virus variants, restriction policies or vaccines. The short-term relationship between the infection maximum increase and demographic, pollution and meteo-climatic parameters was investigated, including both winter-spring and summer 2020 data, also focusing separately on the two seasonal periods and on North vs Centre-South. Among main results, the importance of population size confirmed social distancing as a key management option. The pollution hazardous role undoubtedly emerged, as NO_2 affected infection increase in all the studied scenarios, $PM_{2.5}$ manifested its impact in North of Italy, while O_3 always showed a protective action. Whereas higher temperatures were beneficial, especially in the cold season with also wind and relative humidity, solar irradiance was always relevant, revealing several significant interactions with other co-factors. Presented findings address the importance of the environment in Sars-CoV-2 spread and indicated that special carefulness should be taken in crowded areas, especially if they are highly polluted and weakly exposed to sun. The results suggest that containment of future epidemics similar to Covid-19 could be supported by reducing environmental pollution, achieving safer social habits and promoting preventive health care for better immune system response, as an only comprehensive strategy.

1. Introduction

Early phase of SARS-CoV-2 pandemic in Europe started in Italy on January 30th' 2020, giving rise to the so-called 1st wave. Lockdown restrictions were adopted on the whole nation from March to May, when the restrictions were gradually eased because of the important reduction of infections, then the 1st wave was considered ended in June [1].

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This time frame probably represents the most reliable period to be investigated, because many confounding/modifying factors were still absent or mitigated (i.e. vaccination campaign, region-dependent restriction policies, different methodologies for SARS-CoV-2 tests, virus variants leading to different symptomatology and transmissibility [2], etc).

Italy represents an interesting study scenario because of its territorial heterogeneity, in terms of pollution, land morphology, which in turn affects climate variability. In fact, Northern Italy is attached to the European continent and protected from winds by the Alps and Apennine mountains, while the Centre-South is a peninsula dominated mainly by Mediterranean climate and subjected to Atlantic and African winds (Fig. 1). The unbalanced virus spread between the North and the remaining part of the nation addressed many researchers to hypothesize a detrimental effect of long-term pollution on infection probability and/or COVID-19 severity, as the Po Valley is one of the most polluted areas of Europe [3–7]. It is however to consider that other aspects could have mitigated the virus transmission in the South of the nation, as the implementation of mobility restrictions just after the first outbreaks in Lombardy. However, other than the risk due to uncontrolled movements before 'getting locked' [8], it is interesting that also in very crowded southern cities, as Rome or Naples, the virus outbreaks led to a very milder spread, suggesting some other possible unknown protective factors [7]. Another intriguing aspect is the impressing reduction of infections in summer, giving rise to different causal interpretations, as the prolonged lock-down period before summer, the different environmental conditions in terms of both climate and pollution, or the seasonal trends in immunological reactivity that support the view of SARS-CoV-2 as a 'seasonal virus' just like other coronaviruses [9].

Although most of infections happen in indoor settings [10], the role of outdoor pollution and climatic conditions seems ascertained by several ecological studies [11,12]. One reason why exposure to air pollutants and unhealthy climatic conditions could affect viral transmission might rely on the deleterious effects of air pollution on humans, through the weakening of the immune system reaction [4,13] bringing to comorbidities that can rise up the number of symptomatic cases with consequent increases in positive swabs. Also, indoor environments are affected by ambient pollution. While opening windows in temperate and unpolluted areas can improve the indoor environmental quality (IEQ), in polluted areas, pollutants can infiltrate indoors through windows and HVAC systems [14]. That is one of the reasons why a correct design and management (e.g. filtering clean-up frequency and ventilation efficiency) of HVAC systems requires major attention [15,16]. Virus transmission can also occur outdoors, in a lesser extent and especially in case of crowding – e.g. during super-spreading events (sport matches, concerts etc.) [17].

The scientific literature reported different sets of possible determinants to be investigated. Among them, climatic conditions (as temperature, relative humidity, wind, air pressure, solar irradiation) were extensively studied and usually linked to a seasonal pattern of viral spread [9]. For instance, solar irradiation, affects the levels of vitamin D in the body, which helps the immune system response [18]. Among majorly studied pollutants, NO_2 and PM were frequently associated to increases in COVID-19 infections, the first because of its interaction with alveolar cells, the second by triggering the inflammatory response just like SARS-CoV-2, thus increasing cardio-respiratory risk [16,19]. Irritants for the lungs are also SO_2 and O_3, leading to controversial findings in the literature [5,20–22]. Other factors can affect SARS-CoV-2 infection, as people size and density, the social behaviour of people (e.g. family size, people standing alone, vehicular mobility), vulnerability (age, oldness index, gender) [6]. In previous findings, population size and density

Fig. 1. Selected capital provinces on the Italian territory (created by internet application Google Maps, Alphabet Inc. - Mountain View, CA).

were contradictorily linked to Covid-19 spread, as these variables can involve socio-economic factors, restriction policies and cultural compliance to their respect, besides reflecting the probability of interpersonal contacts [23,24]. The altitude and presence of the sea were also considered among the determinants because they can affect pollutant levels and aerosol composition [11,25].

Our work aims to investigate environmental and human factors that could have affected the spread of Covid-19. As a novelty of the study, the focus was on the difference in the impact of the virus depending on the geographical area as well as on the time of the year, trying to highlight area- and time-specific determinants. In detail, the main determinants concurring in infection spreading were investigated during the early pandemic phase in 57 Italian provinces (Fig. 1) including also the summer period, and investigated the previous environmental conditions, including pollutant concentrations ($PM_{2.5\text{-}10}$, $PM_{2.5}$, O_3, SO_2 and NO_2) and climatic factors (temperature (T), solar irradiance (IR), wind speed (WS) and relative humidity (rH)), and controlling for demographics characteristics (number of province inhabitants, population density *etc.*) and vehicular mobility. This research focused on short-term correlations, so the time of the maximum increase of positive cases (MaxΔ+) was deemed as a good proxy of the infectious trend. This choice allowed to disregard some important latent factors (i.e. socioeconomic status, symptom gravity, comorbidities, quality of local sanitary system), as it simply represents the maximum strength of the virus spread in a well-defined area and investigated the preceding environmental conditions. Moreover, it is not directly related to incidence, as it represents the maximum positive variation of confirmed cases during a defined period, so the size of related province population was tested as a possible determinant factor. Daily determinant data were recorded and averaged in the days from 20 to 14 before the MaxΔ+[7]. This (14–20)-day lag period was chosen starting from the known average incubation phase of 6/7 days with a range between 1 and 14 days [26], and considering the time needed to perform the PCR test, get the positive result and communicate it to central authority, a latency period of two weeks (i.e. 14 days) before the moment of the MaxΔ+ was considered reasonably correct. Finally, the MaxΔ+ was averaged on a three-day period, to account for possible delays in the communication process from local to central authorities and reduce overestimation, especially after the weekend (3d-MaxΔ+). Thus, briefly the dependent variable represents the peak of new infections (one during the 1st wave and one during summer) (averaged on the 3 day before the peak) for each selected province, that was studied in association with potential determinants collected with a 2-weeks lag.

The study aims to highlight: 1. the statistically-significant relationships between the outcome and potential determinants considered on the whole, 2. the period-specific factors, concurring in so different pandemic scenarios, studying the cold and warm season separately (1st wave vs summer), so freezing the effect of the restriction policy of the 1st wave on the summer (as the relationship between the MaxΔ+ and the 14-20-lagged determinant factors cannot be affected by the trend of the previous months), 3. the impact of different pollution levels and climatic factors on confirmed positive cases in the two areas of Italy, by splitting the territories included at the borders of the Po valley from the remaining part of the nation (North vs Centre-South). The applied statistical approach investigated, into the same picture, the contribution of different factors considered together, identifying the most impacting on virus spread, starting from a single-determinant selection, then assessing their overall contributions to the variability of the outcome. Finally, the applied mixed model allows accounting for latent factors, linked to specific regional scenarios (including regional specific policies added to the national regulation, heterogeneity of people habits, cultural and socioeconomic status, etc.).

2. Methods

2.1. Data collection

The study involved 57 Italian province capitals, at least two for each region (if present), always including the region capitals while the others were randomly selected. Province position on the national territory is graphically depicted in Fig. 1. The study was focused on MaxΔ+ (i.e. the maximum increase of confirmed cases, identified among daily data of new cases, communicated by the provinces to the Italian National Institute of Health [27]. Infected persons were recognized by a positive nasopharyngeal swab with a real-time PCR process. This approach remained unchanged for the different phases of the pandemic considered in this study, as antigen tests were included in the count starting only from January 2021 [28].

To include accumulation effect due to possible delays in the communication process, caused by the high pressure of the emergency or for organizational issues, the MaxΔ+ was averaged including cases of the two days before the peak. This approach reduced the possible overestimation of the number of the maximum number of registered new positives (3d-MaxΔ+).

The 3d-MaxΔ+ was established in relation to two different periods: the first ranged from the start of the pandemic to the end of spring (i.e. from February 20th to June 20th, 2020, briefly called ‘1st Wave’), while the second period included the entire summer (21st June to 21st September, i.e. ‘Summer’).

As mentioned, daily data of determinants were recorded in the days from 20 to 14 before the MaxΔ+. This lag was selected taking into account the mean incubation period and the time required to perform the PCR test and obtain the positivity result. In detail, for the summer, if the period of data collection fell in the spring, due to considered temporal lag (i.e. before June 21st), the successive peak was studied, in order to don’t overlap infections still linked to the ‘1st wave’.

All collected data were publicly available data, except for irradiance. Demographic data were retrieved from the official website of the Italian National Institute of Statistics referring to 2019 data [29]. Demographic characteristics were the number of inhabitants of the province, population density (resident inhabitants per km [2]), mean age (weighted on the population number in each age class), gender (expressed as percentage of males on total province population), index of oldness (defined as number of people >65 years old/nr of people 0–14 years old)*100), family size (number of persons belonging to the same residential unit), number of persons living alone (unipersonal family).

Environmental pollution data concerned daily levels of PM_{10}, $PM_{2.5}$, O_3, SO_2 and NO_2, and were obtained from public databases managed by the Regional Environmental Protection Agencies. In order to assess the impact of coarse particles, the concentration of the $PM_{2.5-10}$ fraction was calculated by subtraction of $PM_{2.5}$ from PM_{10}.

The average daily data regarding T, rH, WS and IR, were retrieved by the databases mentioned above, when available, otherwise by free public websites [30].

Daily values of irradiance were kindly furnished by the meteorological service of Italian Military Airforce ("Centro Operativo per la Meteorologia (COMET)"), that is supported by EUMETSAT, responsible of data and satellite service in Italy. Irradiance was provided by Daily Surface Solar Irradiance (netCDF), that furnishes an estimate of the daily solar irradiance reaching the Earth surface, derived from the 0.6 μm visible channel of SEVIRI on board the geostationary satellite Meteosat. The integration of all the hourly values in the UT day allows obtaining the daily value, that is then remapped onto a 0.05° regular grid and data are reported in function of longitude and latitude [31].

Vehicle mobility was expressed as the percentage of variation in traffic volume with respect to a baseline period (i.e. January 13th to 16 February 16th' 2020). These data were obtained by an interactive mobility map, implemented by Enel X with HERE Technologies, in order to depict the trend of different parameters, as the percentage variation in macro-mobility flux of trips compared to well defined periods, with data available in regional, province and municipal scale and updated daily [32].

Territorial characteristics included in the analysis as covariates were altitude and presence of the sea on the capital province coast.

Geographically, the 'North' area was identified by regions included among the Alpine arch, the Po Valley and the Apennine chain, so covering the provinces of Val d'Aosta, Piedmont, Lombardy, Veneto, Trentino, Friuli-Venezia Giulia, Emilia-Romagna regions, while the 'Central-South' area involved all provinces of the remaining territory.

2.2. Statistical analysis

The p-value cut-off for significance was set at 0.05. The statistical software used was SPSS.27 (IBM Corp., Armonk, NY, USA).

The outcome was tested for normality by Kolmogorov-Smirnov test and data log-transformation was performed to achieve a $\log_e$-normal distribution and reduce heteroscedasticity. Daily continuous determinants were represented by the average value on the monitoring week. Descriptive statistics of the outcome and of the potential determinants was performed (Tables 1–3). Parameters were also tested for difference between the two monitoring periods by Wilcoxon test or t-paired test, and the two geographic areas by Mann-Whitney test or by *t*-test, depending on the data distribution, if parametric or not.

Association of potential determinants to the outcome was assessed by linear mixed models for repeated measurements (LMM). This approach allows to correctly model the cross-sectional repeated observation design. Mathematically, the model can be briefly synthetized by the expression: $Y_i = X_i\beta_i + Z_iu_i + \varepsilon_i$ where $i = 1, \ldots, n$ is the case number ranging among the n provinces ($n = 57$), Y_i represents the studied dependent variable (3d-MaxΔ+), X_i is the fixed effects matrix of the study and β_i the fixed effect vector (underlying the tested independent variables), while Z_i is the random effect matrix of the study and u_i is the random vector (i. e. belonging regions), with ε_i representing the residuals [14].

Indeed, as the study considered the same variables in the same set of provinces (subjects), repeated in two different temporal scenarios (i.e. the 1st wave and the summer period), the statistical model has to take into account the inter-variability between provinces (i.e. different associations to the potential determinants) and the intra-variability of the same province between the two moments of monitoring, which is expected to give site-specific dependent associations. Moreover, the study design contains a multilevel structure, as different provinces belong to the same region, and each region is considered to have unmeasured latent factors (i.e. different restrictions due to pandemic, industrialization or agricultural prevalence, occupational issues, population habits, specific management of emergency and organizational issues in Covid-19 test performing and communication to the ISS, etc.): so the regions, where the provinces are located, were included as random factors.

Interactions among determinants were tested, always including in the model main effects, even not significant [33]. As generally adopted, variables were 'centered' by subtracting the mean from each score, yielding a 'centered score' [34], and standardized Z

Table 1
Descriptive statistics for the number of the maximum increase of positive cases (MaxΔ+) for each studied province capital and the average over 3-days including the MaxΔ+ day (3d-MaxΔ+). Results are summarized for the total sample, the two studied periods separately (1st Wave and summer) with significant difference reported by p-value of Wilcoxon or t-paired test, and geographic position (North and Centre-South) with significant differences reported by p-value of Mann-Whitney or *t*-test (depending on data distribution).

Outcome	n	Arithmetic Mean ± S.D.	Median [IQR]	Min-Max	p-value 1^{st}W vs S	p-value N vs C–S
MaxΔ + (Maximum increase of new positive cases) (n)						
Total	114	93.2 ± 141.0	45 [87]	4–868	<0.001	0.002
1st Wave	57	146.0 ± 180.9	80.0 [119]	10–868		<0.001
Summer	57	40.5 ± 41.1	27.0 [38]	4–185		0.732
North	46	142.8 ± 186.3	78 [145.3]	4–868		
Centre-South	68	59.7 ± 85.9	31.5 [56.0]	4–628		
3d-*MaxΔ*+ (Average of cases including 3-days from *MaxΔ*+) (n)						
Total	114	54.9 ± 85.6	25.3 [520]	1.3–521.3	<0.001	0.002
1st Wave	57	85.2 ± 109.3	49.3 [83.5]	4.0–521.3		<0.001
Summer	57	24.7 ± 31.1	12.3 [25.7]	1.3–151.0		0.678
North	46	85.9 ± 116.6	40.3 [83.3]	1.7–521.3		
Centre-South	68	34.0 ± 46.0	16.2 [30.9]	1.3–287.0		

Table 2
Descriptive statistics for demographic and geographical parameters. Results are summarized for the total sample, the two studied periods separately (1st Wave and summer) with significant difference reported by p-value of Wilcoxon or t-paired test, and geographic position (North vs Centre-South) with significant differences reported by p-value of Mann-Whitney or *t*-test (depending on data distribution).

Potential determinants	N	Arithmetic Mean ± S.D.	Median [IQR]	Min-Max	p-value N vs C–S
Demographics					
% males vs 100 females	57	48.8 ± 0.5	48.9 [0.8]	47.7–49.8	0.193
North	23	48.9 ± 0.4	49.0 [0.7]	48.0–49.6	
Centre-South	34	48.8 ± 0.5	48.8 [0.8]	47.7–49.8	
Nr hinabitants (thou)	57	703.3 ± 799.8	430.9 [660.3]	32.8–4333.3	0.248
North	46	755.7 ± 730.4	532.1 [627.0]	125.5–3280.0	
Centre-South	68	667.8 ± 852.3	429.6 [583.1]	32.8–433.3	
Population density (n/Km^2)	57	309.3 ± 439.7	219.0 [228.0]	49.0–2615.0	0.202
North	23	343.1 ± 437.0	275.0 [234.0]	57.0–2082.0	
Centre-South	34	286.3 ± 446.6	187.0 [219.0]	49.0–2615.0	
Average age (y)	57	46.1 ± 1.7	46.2 [2.1]	42.1–49.2	0.974
North	23	46.2 ± 1.5	46.2 [1.8]	43.0–49.2	
Centre-South	34	46.0 ± 1.8	46.2 [2.2]	42.1–49.2	
Oldness index (%)	57	191.4 ± 36.1	190.4 [42.7]	121.5–212.8	0.235
North	23	187.2 ± 34.3	184.7 [36.5]	126.6–263.8	
Centre-South	34	194.2 ± 37.5	195.7 [44.1]	121.5–272.8	
Family size (n)	57	2.3 ± 0.1	2.3 [0.2]	2.0–2.7	0.002
North	23	2.2 ± 0.1	2.3 [0.2]	2.0–2.4	
Centre-South	34	2.4 ± 0.1	2.4 [0.2]	2.0–2.7	
People standing alone (n)	57	549.3 ± 413.2	553.0 [504]	32.0–1499.0	0.001
North	23	780.6 ± 491.8	723.0 [883.0]	32.0–1499.0	
Centre-South	34	392.9 ± 256.9	309.0 [388.0]	47.0–936.0	
Geomorphologic characteristics					
Altitude	57	174.7 ± 233.8	54.0 [269.5]	2.0–931.0	1.000
North	23	133.6 ± 161.2	61.0 [177.0]	2.0–583.0	
Centre-South	34	202.5 ± 271.2	40.0 [393.5]	3.0–931.0	
Province coasting sea	57	23 (40.4%)	–	–	0.235
North	23	3 (13.0%)	–	–	
Centre-South	34	20 (58.8%)	–	–	

models were performed, in order to achieve better understanding of results (estimate and significance reported as b_Z and p_Z). The modification of the effect on the outcome of interacting variables was graphically addressed by the Simple-Slope method, that allows to study the relationship grouping the 'moderator' (or interacting variable) in terms of ±1 SD (Figs. 4 and 5) [35].

The statistical approach comprises the bivariate analysis of 3d-MaxΔ+ versus its potential determinants, which were tested singularly (estimate and significance reported as b_{biv} and p_{biv}) (Table 4). Then, only the ones presenting a significant association were included in the multi-determinant models, using a backward stepwise approach. Rival models were compared by the Akaike and Bayesian Information Criteria, based on the restricted maximum likelihood estimation (AIC and BIC), the lower the better will be the fitting (with a threshold in difference between models <2) and the unstructured covariance matrix for repeated measures was chosen [36]. Collinearity of determinants was tested by the evaluation of the Variance Inflaction Factor (VIF), with a cut-off of 1.5.

The study of determinants, both seasonal (i.e. 1st Wave and Summer) and geographic (i.e. North and Centre-South), was carried out applying the same statistical approach.

As environmental data were sometimes unavailable, missing data were assigned by multiple imputation (MI) if present in at least 20% of cases. Ten imputations were obtained by an iterative Markov Chain Monte Carlo method, using available predictors showing a very strong association ($R > 0.85$) and confirmed by scientific knowledge. Missing data were excluded by MI when no predicting factors for imputation were available. The average of the assigned values was then included in the dataset. The use of multiple imputation was aimed to diminish loss of information on other parameters included in the model owing to the reduced statistical power. For this reason, dataset completed by MI was used in the only multivariate statistical models, and missing values were left in descriptive and bivariate analysis.

3. Results and discussion

Data were completely collected for every data-set except for environmental pollutants, which had 26.3% missing data for SO_2, 15.8% for $PM_{2.5}$, 2.6% for PM_{10} and 5.3% for O_3; in only one case air pollution data were unavailable (i.e. Autonomous Province of Bolzano-South Tyrol). SO_2 was analyzed for descriptive statistics and bivariate models, but it was excluded from MI process in multi-determinant models, as missing data exceeded the defined cut-off (20%).

Descriptive statistics of the outcome are reported in Table 1 and graphically represented by map clustering in Fig. 2(a and b), showing significantly higher 3d-MaxΔ+ in the North of the nation during the 1st wave (Fig. 2(a)), and a drastic reduction in the summer period (Fig. 2(b)).

Potential determinants are shown in Tables 2 and 3, while Tables 4 and 5 summarize single- and multi-determinant linear mixed models, with model coefficients estimates representing b_{biv} in Table 4 and b_Z in Table 5. Interaction terms are graphically depicted in

Table 3
Descriptive statistics for environmental pollutants, meteorological parameters and vehicular mobility. Results are summarized for the total, the two studied periods separately (1st Wave and summer) with significant difference reported by p-value of Wilcoxon or t-paired test, and geographic position (North and Centre-South) with significant differences reported by p-value of Mann-Whitney or *t*-test (depending on data distribution).

Potential determinants	n	Arithmetic Mean ± S.D.	Median [IQR]	Min-Max	p-value 1stW vs S	p-value N vs C–S
Environmental pollutants						
$PM_{2.5}$ (μg/m^3)						
Total	96	12.1 ± 5.3	11.9 [6.3]	3.2–32.9	<0.001	0.053
1st Wave	48	14.0 ± 6.1	13.1 [9.0]	3.2–32.9		0.001
Summer	48	10.1 ± 3.6	9.2 [5.2]	3.4–21.0		0.544
North	36	13.4 ± 5.3	12.9 [9.5]	4.9–25.7		
Centre-South	60	11.3 ± 5.3	11.0 [5.3]	3.2–32.9		
$PM_{2.5\text{-}10}$ (μg/m^3)						
Total	110	7.7 ± 4.2	7.1 [4.6]	1.3–27.3	0.378	0.559
1st Wave	56	7.6 ± 4.8	6.8 [5.0]	1.3–27.3		0.268
Summer	54	7.8 ± 3.5	7.4 [4.1]	1.4–16.1		0.716
North	43	7.8 ± 3.7	6.9 [5.1]	1.3–20.5		
Centre-South	67	7.7 ± 4.5	7.1 [3.4]	1.4–27.3		
NO_2 (μg/m^3)						
Total	112	24.5 ± 13.2	21.8 [17.8]	3.0–60.9	0.004	0.819
1st Wave	56	28.2 ± 14.3	27.3 [20.6]	6.3–60.9		0.597
Summer	56	20.7 ± 11.0	17.4 [13.9]	3.0–55.4		0.330
North	44	23.6 ± 11.2	21.9 [14.7]	7.7–57.0		
Centre-South	68	25.1 ± 14.5	21.2 [20.0]	3.0–60.9		
O_3 (μg/m^3)						
Total	108	75.1 ± 24.7	79.9 [33.2]	24.9–128.1	<0.001	0.030
1st Wave	55	65.2 ± 22.7	71.7 [45.1]	24.9–104.3		0.002
Summer	53	85.4 ± 22.4	89.0 [30.2]	29.6–128.1		0.563
North	42	67.7 ± 26.5	72.7 [49.8]	24.9–112.9		
Centre-South	66	79.8 ± 22.4	83.5 [29.3]	29.6–128.1		
SO_2 (μg/m^3)						
Total	84	3.2 ± 2.5	2.8 [2.7]	0.3–16.1	0.549	0.548
1st Wave	43	3.5 ± 3.0	3.0 [3.3]	0.7–16.1		0.559
Summer	41	2.9 ± 2.0	2.7 [2.4]	0.3–8.6		0.831
North	33	3.5 ± 3.0	3.0 [2.9]	0.9–16.1		
Centre-South	51	3.0 ± 2.2	2.7 [2.7]	0.3–10.4		
Meteorological parameters						
T (°C)						
Total	114	17.2 ± 7.8	16.1 [14.9]	2.6–29.4	<0.001	0.014
1st Wave	57	9.9 ± 2.4	10.3 [2.9]	2.6–14.0		<0.001
Summer	57	24.6 ± 2.9	25.1 [4.4]	18.2–29.4		0.055
North	46	15.8 ± 8.3	15.0 [15.8]	2.6–28.7		
Centre-South	68	18.2 ± 7.4	16.1 [14.5]	6.0–29.4		
rH (%)						
Total	114	65.1 ± 9.8	65.1 [13.9]	41.2–90.9	0.267	0.021
1st Wave	57	66.6 ± 9.4	65.0 [14.0]	46.0–90.9		0.276
Summer	57	63.7 ± 10.1	65.1 [14.6]	41.2–81.5		0.018
North	46	68.0 ± 9.8	69.4 [15.9]	49.4–90.9		
Centre-South	68	63.2 ± 9.4	64.0 [10.8]	41.2–80.9		
WS (m/s)						
Total	114	2.2 ± 1.1	2.1 [1.3]	0.4–5.5	0.132	<0.001
1st Wave	57	2.1 ± 1.1	1.8 [1.4]	0.4–5.5		0.055
Summer	57	2.4 ± 1.1	2.1 [1.5]	0.5–5.2		<0.001
North	46	1.7 ± 0.8	1.7 [1.0]	0.4–4.2		
Centre-South	68	2.6 ± 1.1	2.5 [1.4]	0.9–5.5		
IR (MJ/m^2)						
Total	114	14.6 ± 41.0	14.7 [61.0]	39.7–21.8	<0.001	<0.001
1st Wave	57	11.5 ± 29.1	11.8 [38.0]	39.7–17.5		<0.001
Summer	57	17.7 ± 25.1	17.7 [37.5]	11.6–21.8		<0.001
North	46	12.6 ± 41.2	13.0 [73.1]	39.7–20.1		
Centre-South	68	16.0 ± 34.8	16.5 [57.2]	98.3–21.8		
Vehicular mobility vs baseline (%)						
Total	114	−2.9 ± 41	−7.2 [42.1]	−75.0–141.0	<0.001	0.054
1st Wave	57	−30.6 ± 21.2	−23.7 [38.4]	−75.0-(-1.0)		0.929
Summer	57	24.8 ± 37.0	17.6 [32.5]	−51.6–141.0		<0.001
North	46	−11.6 ± 34.3	−12.3 [29.0]	−75.0–141.0		
Centre-South	68	3.0 ± 44.2	−3.4 [54.1]	−68.1–128.7		

Table 4
Linear mixed models for potential single determinant vs MaxΔ+ (average on 3 days, log-transformed) for the whole sample (repeated measurements). The study periods separately (1st Wave and summer) and the geographic position with respect the Apennine chain (North vs Centre-South) (repeated measurements). Results are reported as estimate b_{biv} and p-value.

Single determinant models										
y = Ln (3d-MaxΔ+)	**Total**		**1st Wave**		**Summer**		**North**		**Centre-South**	
	b_{biv}	*p-value*	b_{biv}	*p-value*	*bbiv*	*p-value*	b_{biv}	*p-value*	b_{biv}	*p-value*
Demographic characteristics										
% males	−0.070	0.806	−0.008	0.980	−0.120	0.707	0.337	0.411	−0.511	0.138
Nr inhabitants	0.001	<0.001	0.001	<0.001	0.001	<0.001	0.001	<0.001	0.001	<0.001
Population density	0.001	0.001	0.001	0.017	0.001	0.001	0.001	0.074	0.001	0.008
Average age	−0.095	0.234	−0.011	0.911	−0.156	0.079	−0.230	0.043	0.002	0.987
Oldness index	−0.007	0.048	−0.006	0.197	−0.008	0.038	−0.010	0.044	−0.003	0.571
Family size	−1.198	0.209	−2.785	0.011	0.469	0.661	3.222	0.078	−1.411	0.215
People alone	0.001	<0.001	0.002	<0.001	0.001	0.095	0.001	0.001	0.002	0.015
Geomorphologic characteristics										
Altitude	−0.002	0.005	−0.001	0.063	−0.002	0.004	−0.001	0.457	−0.001	0.027
Coasting sea	−0.019	0.945	−0.580	0.065	−0.445	0.140	−0.681	0.175	0.652	0.053
Environmental pollutant (µg/m3)										
$PM_{2.5}$	0.092	<0.001	0.062	0.023	−0.023	0.628	0.179	<0.001	0.022	0.358
$PM_{2.5\text{-}10}$	−0.038	0.206	−0.008	0.808	−0.066	0.140	−0.016	0.722	−0.047	0.082
NO_2	0.041	<0.001	0.026	0.019	0.029	0.035	0.062	0.001	0.029	0.002
O_3	−0.034	<0.001	−0.028	<0.001	−0.002	0.823	−0.032	<0.001	−0.018	0.005
SO_2	−0.005	0.936	−0.018	0.792	−0.109	0.229	−0.029	0.658	−0.015	0.839
Meteorologic parameters										
T (°C)	−0.084	<0.001	−0.234	<0.001	−0.023	0.663	−0.123	<0.001	−0.049	<0.001
rH (%)	0.026	0.033	0.026	0.124	0.012	0.434	0.027	0.162	0.010	0.454
WS (m/s)	−0.292	0.009	−0.294	0.044	−0.181	0.183	−0.262	0.232	−0.161	0.136
IR (MJ/m^2)	−0.175	<0.001	−0.183	<0.001	−0.045	0.457	−0.237	<0.001	−0.104	<0.001
Vehicular mobility (%)										
vs baseline	−0.013	<0.001	−0.003	0.887	−0.010	0.004	−0.017	0.003	−0.009	<0.001

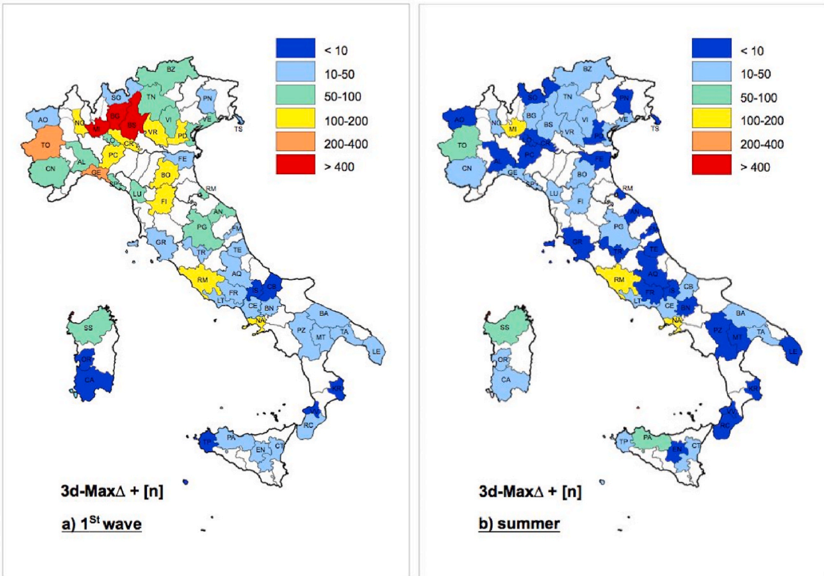

Fig. 2. Map clustering of the study outcome (3d-MaxΔ+)[n] for the selected capital provinces during (a) the 1st wave and (b) the summer. The maps were generated with Archicad v.18.

Figs. 4–5 and the statistical parameters referred to ±1SD of the interaction terms are indicated by Z/±1SD.

3.1. Demographic determinants

Demographic parameters showed an important effect on the outcome in single-determinant models. The crucial parameter was the province population size, visually represented in Fig. 3, as our data showed that high-population provinces had higher increases of

Table 5
Multi-determinant linear mixed models for standardized maximum increase of cases (average on 3 days, log-transformed) for the whole sample (repeated measurements), the study periods separately (1st Wave and summer) and the geographic position (North vs Centre-South) (repeated measurements). Results are reported as estimate b_Z, confidence interval and p value. All variables were standardized. Models with difference in AIC or BIC <2 were reported as equivalent.

Multi-determinant models: y = Z Ln (3d-MaxΔ+)						
Total (N = 112, Subj = 56)						
	AIC = 213.6; BIC = 243.5					
	b_Z	**CI 95%**	**p-value**			
Nr inhabitants (K)	0.502	(0.374; 0.629)	<0.001			
NO2 (μg/m3)	0.169	(0.043; 0.295)	0.009			
O3 (μg/m3)	−0.196	(-0.335; −0.057)	0.006			
T (°C)	−0.259	(-0.463; −0.056)	0.013			
IR (MJ/m2)	−0.135	(-0.345; 0.075)	0.206			
IR * + 1DS(T)	0.076	(-0.189; 0.341)	0.569			
IR* -1DS(T)	−0.345	(-0.564;-0.126)	0.002			
1st wave (N = Subj = 56)						
	AIC = 88.3; BIC = 114.6			**AIC = 89.3; BIC = 113.6**		
	b_Z	**CI 95%**	**p-value**	**b_Z**	**CI 95%**	**p-value**
Nr inhabitants (K)	0.279	(0.149; 0.408)	<0.001	0.267	(0134; 0.400)	<0.001
Family size	−0.196	(-0.333; −0.059)	0.006	−0.269	(-0.401;-0.136)	<0.001
NO2 (μg/m3)	0.241	(0.124; 0.358)	<0.001	0.429	(0.231; 0.626)	<0.001
O3 (μg/m3)	−0.329	(-0.478; −0.180)	<0.001	−0.410	(-0.564; 0.256)	<0.001
T (°C)	−1.173	(-1.829; −0.518)	0.001	−1.213	(-1.869;-0.556)	<0.001
T * + 1DS (rH)	−1.852	(-2.597;-1.107)	<0.001	–	–	–
T * -1DS (rH)	−0.495	(-1.324; 0.334)	0.237	–	–	–
IR (MJ/m2)	−1.189	(-1.804;-0.574)	<0.001	−0.763	(-1.406;-0.133)	0.021
IR * + 1DS(T)	−2.122	(-3.259;-0.984)	<0.001	−1.461	(-2.649; −0.273)	0.017
IR* -1DS(T)	−0.256	(-0.487;-0.024)	0.031	−0.065	(-0.302; 0.173)	0.588
IR *+1DS(NO2)				−0.468	(-1.211; 0.276)	0.213
IR * -1DS(NO2)				−1.058	(-1.673;-0.442)	0.001
WS (m/s)	−0.142	(-0.269;-0.015)	0.029	−0.138	(-0.269;-0.006)	0.040
rH (%)	−0.730	(-1.188;-0.272)	0.002	–	–	–
Summer (N = Subj = 57)						
	AIC = 108.3; BIC = 122.6					
	b_Z	**CI 95%**	**p-value**			
Nr inhabitants (K)	0.600	(0.451; 0.750)	<0.001			
O3 (μg/m3)	0.280	(-0.034; 0.594)	0.079			
IR (MJ/m2)	−0.032	(-0.294; 0.229)	0.805			
IR * + 1DS(O3)	−0.416	(-0.782;-0.050)	0.027			
IR * -1DS(O3)	0.351	(-0.072; 0.775)	0.102			
North (N = 46; Subj = 23)						
	AIC = 71.1; BIC = 92.5			**AIC = 72.2; BIC = 93.6**		
	b_Z	**CI 95%**	**p-value**	**b_Z**	**CI 95%**	**p-value**
Nr inhabitants(K)	0.401	(0.189; 0.613)	0.001	0.461	(0.245; 0.678)	<0.001
PM2.5 (μg/m3)	0.372	(0.242; 0.501)	<0.001	0.343	(0.196; 0.489)	<0.001
NO2 (μg/m3)	0.411	(0.072; 0.749)	0.019	0.386	(0.196; 0.489)	0.023
O3 (μg/m3)	−0.498	(-0.669;-0.326)	<0.001	−0.325	(-0471;-0.178)	<0.001
IR (MJ/m2)	−0.159	(0.334; 0.015)	0.072	−0.152	(-0.346;-0.041)	0.119
IR *+1DS(NO2)	0.355	(-0.042; 0.752)	0.078	0.335	(-0.068; 0.739)	0.101
IR * -1DS(NO2)	−0.674	(-0.851;-0.497)	<0.001	−0.640	(-0.837; −0.443)	<0.001
IR * + 1DS(O3)	−0.301	(-0.483;-0.118)	0.002	–	–	–
IR * -1DS(O3)	−0.018	(-0.235; 0.198)	0.862	–	–	–
Mobility (%)	–	–	–	−0.166	(-0.328; −0.003)	0.046
Centre-South (N = 68; Subj = 34)						
	AIC = 138.3; BIC = 156.1			**AIC = 137.4; BIC = 166.4**		
	b_Z	**CI 95%**	**p-value**	**b_Z**	**CI 95%**	**p-value**
Nr inhabitants (K)	0.457	(0.289;0.625)	<0.001	0.441	(0.284; 0.597)	<0.001
NO2 (μg/m3)	0.172	(0.401;0.323)	0.027	0.197	(0.044;0.349)	0.013
O3 (μg/m3)	-	-	-	−0.198	(-0.383; -0.014)	0.036
T (°C)	−0.265	(-0.020; -0.323)	<0.001	-	-	-
IR (MJ/m2)	-	-	-	−0.221	(-0.399;-0.044)	0.016

positive cases. As showed in Table 2, it resulted comparable in the two considered macro-areas ($p = 0.248$), together with population density ($p = 0.202$), and it was strongly linked to the outcome either in the single- ($b_{biv} = 0.001$, $p_{biv}<0.001$) or in the multi-determinant model ($b_Z = 0.502$, $p_Z < 0.001$), both in the North ($b_Z = 0.401 \div 0.461$, $p_Z<=0.001$) and in the Centre-South of Italy ($b_Z = 0.442 \div 0.457$, $p_Z < 0.001$), both in summer ($b_Z = 0.600$, $p_Z < 0.001$) and in the 1st wave ($b_Z = 0.279 \div 0.276$, $p_Z < 0.001$). This reflects the importance of inter-relationship between persons and the difficulties in physical distancing among subjects living in high-density population areas, as reported by Boterman et al. [17]. Interestingly, in the Centre-South and in summer, that is the lower

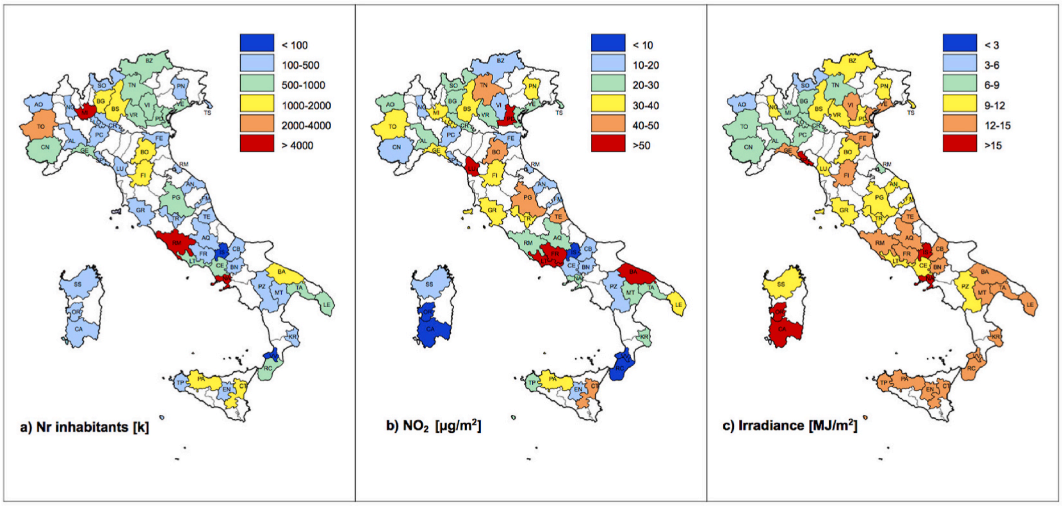

Fig. 3. Map clustering of (a) the inhabitant number [thou], (b) NO2 [μg/m^3], (c) solar irradiance [MJ/m^2] for the selected capital provinces during the 1st wave. The map was generated with Archicad v.18 (https://graphisoft.com/).

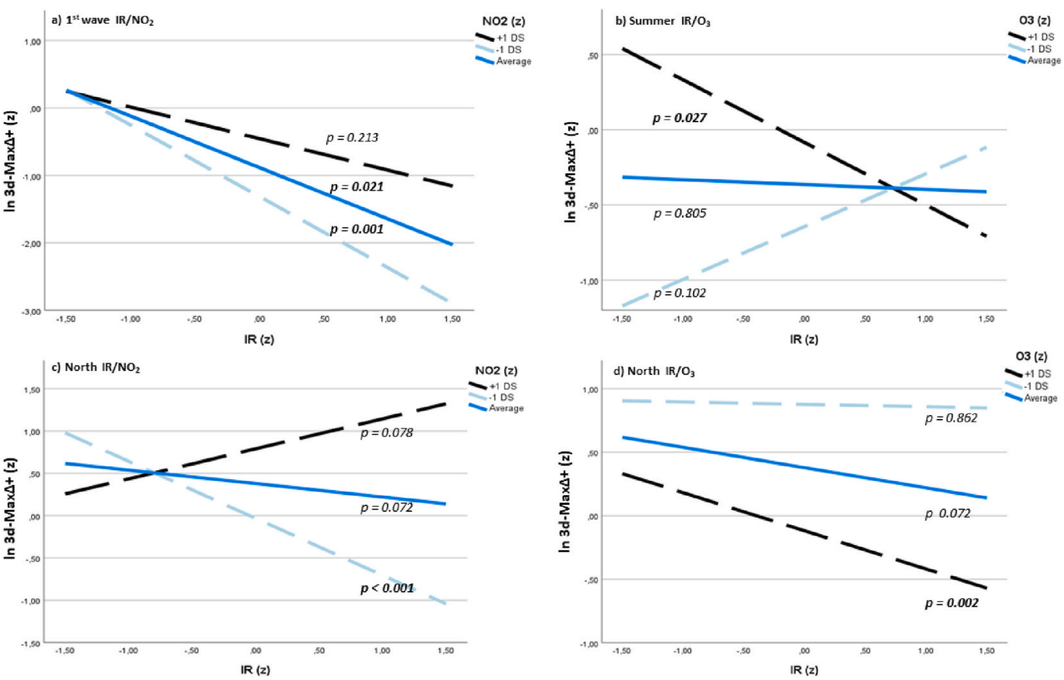

Fig. 4. (a-b-c-d) Simple slope graphs for significant interaction terms between irradiance and co-pollutants vs the outcome (ln 3d-MaxΔ+ (z)): (a) during 1st wave with NO_2, (b) in summer with O_3, in North of Italy (c) with NO_2 and (d) with O_3. All variables are standardized.

pollution period, this was the most impacting determinant. Also, population density, typically used as a surrogate for the inter-relationships among persons, was significant in single-determinants models excluding the North ($b_{biv} = 0.001$; $p_{biv} = 0.001–0.074$), but it loses significance when other predictors were included. Familiar size, greater in the Centre-South ($p = 0.002$), was inversely associated with 3d-MaxΔ+ during the only 1st wave, also in multi-determinant models ($b_Z = -0.196$; $p_Z = 0.006$), suggesting a relationship with lockdown-related behaviors: as the kindergartens and schools were closed, parents of infants/children/teen-agers were prevented from going to work physically, because of take care of children, and working from home was more likely than for single or couples, ensuring them greater isolation from people outside the family unit. In addition, severe Covid-19 disease was very rare for young people/children [37], so the presence of a high family size may also be related to a higher number of asymptomatic or mild symptomatic patients, who did not undergo a diagnostic swab, especially in the 1st wave, because of the sanitary stress. These considerations are confirmed by the result that, in single-determinant models only, the number of people living alone, significantly higher

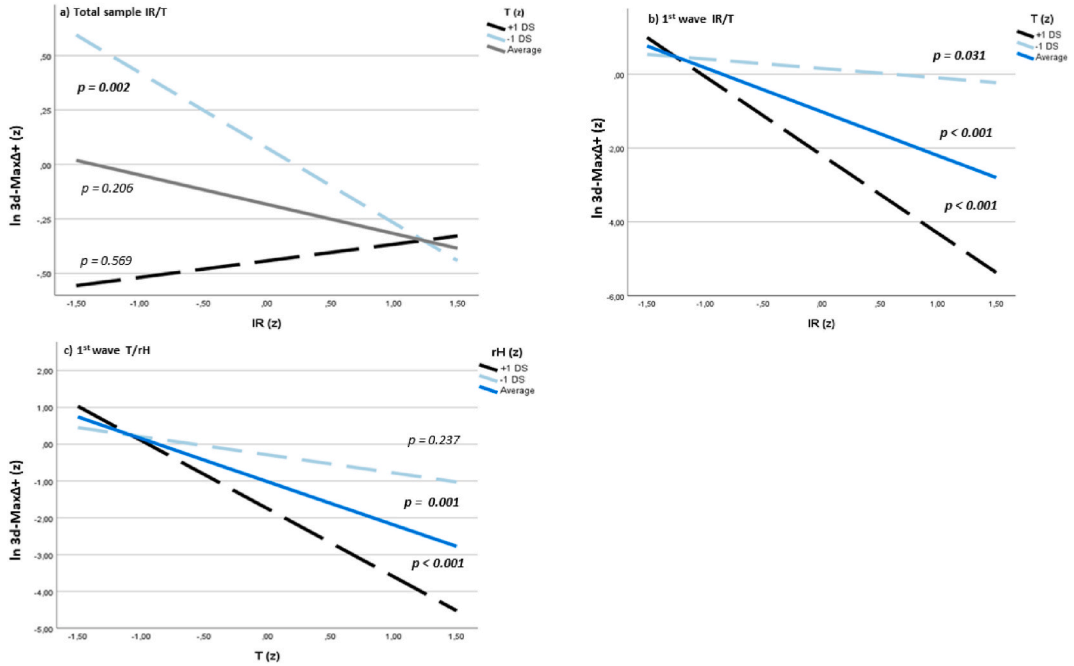

Fig. 5. (a-b-c) Simple slope graphs for significant interactions among the outcome (ln 3d-MaxΔ+ (z)) and meteo-climatic parameters: (a) IR with T in the total sample (1st wave + Summer), during 1st wave (b) IR with T and (c) T with rH. All variables are standardized.

in the North ($p = 0.001$), was associated to the increase of the number of cases ($b_{biv} = 0.001 \div 0.002$, $p_{biv} \leq 0.001 \div 0.095$). Average age, comparable in the two subgroups ($p = 0.974$), was linked to a reduction of cases in the North of Italy ($b_{biv} = -0.230$; $p_{biv} = 0.043$), as younger was the population, more interrelationship due to job or recreational activities was probable. Similarly, provinces with higher percentage of persons more than 70-years old, which presented a comparable distribution in the studied macro-areas ($p = 0.235$), were less prone to get infection (to be distinguished from mortality), as the retirement allowed them to avoid the exposure due to working activity and to conduct a more prudent life-style, also because of the deterrent effect played by the enhanced severity of COVID-19 in the elderlies ($b_{biv} = -0.003 \div -0.010$; $p_{biv} = 0.038 \div 0.197$). This was confirmed by the lack of significance during the 1st wave, as the lockdown restrictions resulted also in a conspicuous number of workers remaining at home. Gender distribution, comparable in North and Centre-South ($p = 0.193$), was not found to be related to differences in contagious increase. This result is coherent with official reports of Istituto Superiore di Sanità, that indicates only a slight higher percentage of infected females (51.1%) compared to males (48.9%) [38]. Vehicle mobility was significantly lower in the 1st wave than in the summer period ($p < 0.001$), because of the restriction policy, especially in the North of Italy ($p = 0.014$). Its increase was linked to a reduction of cases in all the considered scenarios ($b_{biv} = -0.013 \div -0.017$; $p_{biv} < 0.001 \div 0.004$), except for the 1st wave ($p_{biv} = 0.887$), when lockdown restrictions were in force. Interestingly, during summer, when all the restrictions were homogeneously abandoned in the whole nation, a reduction of 3d-MaxΔ+ was related to an increase of vehicular mobility ($b_{biv} = -0.010$; $p_{biv} = 0.004$). Similarly, in multi-determinant models, in the northern area, where public transport are widely utilized and commuting is a frequent working condition [39], its increase results in a protective effect ($b_Z = -0.166$, $p_Z = 0.045$). So, this result can be conceivably linked to the shift to the use of private cars, instead of public transfer vehicles, that can be assumed as an indirect indicator of a reduction potential of infection contexts.

All these population characteristics coherently showed the very important effect of people behavior on the virus spread, most of them remaining significant also in summer, when most part of pollutants and meteorological parameters, very important during the 1st wave, lost their impact. However, as already underlined [7], spread was very different also in big province capitals, (i.e. Rome, Naples, Palermo), requiring to focusing the investigation also on potential environmental determinants.

3.2. Pollution determinants

In our study, almost all the considered pollutants were associated to the outcome but not for the summer period: this lack of correlation could be linked to the reduced variability of pollution on the whole territory (Table 3, Fig. 2(b)) or, on the other hand, to the substantial decrease of infected persons (Table 1). Nevertheless, NO_2 levels remained linked to the variability of the 3d-MaxΔ+ also during summer period, confirming its well-known deleterious effect for human health and suggesting its impact on COVID-19 susceptibility [19,40].

During the warm season, NO_2 outdoor concentration was lower than in the 1st wave ($p = 0.004$), however its effect remains significant in the single determinant model ($b_{biv} = 0.029$; $p_{biv} = 0.035$), and during the 1st wave ($b_{biv} = 0.026$, $p_{biv} = 0.019$). Negligible differences emerged between NO_2 concentrations in the two considered macro-areas ($p = 0.819$), and it remained positively linked to 3d-MaxΔ+ in both North ($b_{biv} = 0.062$; $p_{biv} = 0.001$) and Centre-South ($b_{biv} = 0.029$; $p_{biv} = 0.002$). NO_2 affected the 3d-MaxΔ+ in all the multi-determinant models (excluding summer, with a borderline significance $p_Z = 0.068$). Another interesting result is its modifier effect on irradiance, that was stronger protective for lower levels of NO_2 (-1SD) during the 1st wave and in the northern area ($b_{Z/\text{-}1SD} = -1.058$, $p_{Z/\text{-}1SD} = 0.001$ and $b_{Z/\text{-}1SD} = -0.640$, $p_{Z/\text{-}1SD} < 0.001$, respectively) (Fig. 4a-c), indicating that, when pollution and atmospheric stability are high, the beneficial solar action can be influenced by NO_2 reduction, because of the concurring O_3 production [41], other than the NO_2 absorption itself [42].

The positive association of short-term exposure to NO_2 with COVID-19 incidence rate was already reported elsewhere [4,19,20]. One possible explanation lies on the role of NO_2 exposure in incrementing the activity of Angiotensin-converting-enzyme-2 (ACE2), the SARS-CoV-2 receptor in the alveolar cell [40]. An epidemiological study in the U.S. showed also that long-term exposure to NO_2 can contribute to some extent to severe COVID-19 outcomes, independently from long-term $PM_{2.5}$ and O_3 exposures, making people more biologically vulnerable to COVID-19 and its severe outcomes [43].

Our data indicated that O_3 played a protective role in virus spread. It was higher in summer and in the Centre-South of the nation ($p < 0.001$ and $p = 0.030$), as expected because of its photochemical origin, that depends on solar radiation. Our findings indicated its role in the reduction of 3d-MaxΔ+ in all the considered scenarios and in single-determinant models ($b_{biv} = -0.034 \div -0.018$; $p_{biv} < 0.001 \div 0.005$), excluding summer ($b_{biv} = -0002$, $p_{biv} = 0.823$) (Table 4). Interestingly, in multi-determinant models, during summer it had a crossover interaction with irradiance, with protective impact when, for increasing IR, its levels were high (1SD) ($b_{Z/1SD} = -0.416$, $p_{Z/1SD} = 0.027$) (Fig. 4-b). In all the remaining scenarios, it presented always significant main effect on the outcome ($b_Z = -0.196 \div -0.498$; $p_Z < 0.001 \div 0.036$), and, in the Northern area, similarly to summer, a synergic effect with solar irradiation for its higher levels ($b_{Z/1SD} = -0.301$, $p_{Z/1SD} = 0.002$) (Fig. 4-d). This association can be related to two concurring factors: by one side, ozone concentration is inversely associated to NOx presence, being a product of photochemical reaction of NO_2 itself, even if no higher correlation neither significant interaction terms emerged in the models. On the other side, it is widely used for its virucidal action due to the oxidizing power, which typically inactivates SARS-CoV-2 and other enveloped viruses, causing damages to the viral capsid and genetic material [44] at concentrations much higher than those measured in this study. It could be hypothesized that high short-term outdoor O_3 concentrations could lead to low indoor O_3 levels sufficient to reduce viral viability and SARS-CoV-2 lifetime also in indoor air. Such a finding is not properly in contradiction with the well-known deleterious effect of ozone for human health, because of its irritant action and oxidative stress on the respiratory tract, as the outcome here considered was unrelated to the severity of symptoms or deaths, but to only the 3d-MaxΔ+. Actually, the effect of O_3 short-term exposure on SARS-CoV-2 spread brought to controversial findings. It was linked to an increase of new cases in some studies [5,20,45,46] but all of them analyzed the effect of this pollutant considering a short time-span (1–2 months) during the only lockdown period, when the gradual increase of O_3, reasonably due to the containment measures that reduced the concurrent NOx levels, could result in an apparent positive relationship with pandemic spread [5]. On the other side, Kolluru et 2020 [47] approached the study including pre-lockdown, lockdown and unlocked period (February–June 2020), obtaining the opposite relationship, coherently with our study. Moreover, all the cited studies did not considered multi-determinant models, with controlling factors or interaction terms, and they are sometimes related to very homogeneous or small areas. So, comparison with the current scientific literature can be somewhat misleading.

A largely investigated pollutant was PM, that, in our study, was related to the worsening of the spread of Covid-19. First of all, we found a positive association of 3d-MaxΔ+ with the levels of $PM_{2.5}$, but not for $PM_{2.5\text{-}10}$ (i.e. the only coarse fraction). This was unsurprising as the coarse fraction is unable to reach the lung alveolar region, while the $PM_{2.5}$ is a well-known hazard for human health. This pollutant follows a typical seasonal trend and thus resulted higher during the 1st wave ($p < 0.001$), when was significantly higher in the North ($p = 0.001$). The effect of $PM_{2.5}$ on 3d-MaxΔ+ in single determinant models was always present in the whole sample, during the 1st wave and in the North of Italy ($b_{biv} = 0.062 \div 0.179$; $p_{biv} < 0.001 \div 0.023$), suggesting that $PM_{2.5}$ pollution is someway linked to the outcome when high levels occur. In multi-determinant models, fine PM manifested its worsening impact on the infection spread in the only Northern area ($b_Z = 0.372 \div 0.343$; $p_Z < 0.001$), suggesting that the environmental pollution of the Po valley played a not negligible role in promoting the infection process. These results are coherent with most of previous findings on the relationship between short- and long-term exposure to $PM_{2.5}$ and COVID-19 incidence indicators [3–6,20,47]. It should be noted that our approach did not allow to discern if $PM_{2,5}$ acts as a SARS-CoV-2 carrier or a COVID-19 booster, as the applied statistical method can only reveal the association but not the underlying mechanisms. However, the health impacts of fine PM on the respiratory and cardiovascular systems are well-established [48] and linked to inflammatory response, contributing to the cytokines storms and interacting with the same molecular targets of SARS-CoV-2 [49]. On the other side, the inhalation of saliva aerosol and droplets is of primary importance in COVID-19 infection [50] and thus the presence of SARS-CoV-2 RNA in PM samples is more than expected, especially in indoor environments occupied by positive cases. Some authors have argued that SARS-CoV-2 can be transported via solid aerosols [51,52], but SARS-CoV-2 viability in outdoor aerosols has to be better assessed, as infection through inhalation of SARS-CoV-2 contaminated solid particles is considered very unlikely [53] because of the almost negligible probability of coagulation of virus-laden aerosol with pre-existing atmospheric particles and further inhalation [54], other than of maintaining the virus viable in conditions of high temperature and UV radiation [55].

Even if some studies conducted in other parts of the world indicated that SO_2 was negatively correlated to virus transmission, suggesting a possible anti-viral action [20], no significant association emerged for this pollutant in our study. This is unsurprising, as ambient concentrations of SO_2 are extremely low in Italy and no significant variability resulted in all the considered scenarios ($p > 0.548$).

3.3. Meteorological determinants

A fundamental added value to the overall picture is brought by meteorological parameters, that are well recognized as affecting the vitality of viruses and their spread, and several studies confirmed SARS-CoV-2 does not represent an exception [7,56,57]. Several ecological and epidemiological studies have suggested that COVID-19 could be a seasonal disease, as summer climatic conditions (as warm temperatures, low humidity and higher solar irradiation) can strengthen the immune system response [9].

In our study, the correlation between temperature and irradiance (R = 0.839, VIF = 3.4) complicates the understanding of their concurrent actions. In all the scenarios, except for summer, the two parameters had a direct effect on the outcome in single-determinant models ($b_{biv} = -0.049 \div 0.234$, $p_{biv}<0.001$ for T and $b_{biv} = -0.104 \div 0.237$, $p_{biv}<0.001$ for IR) and maintained a significant relationship in multi-determinant models. Statistically speaking, almost all the models that better fit data contained interaction terms. When considering 1st wave and summer together, temperature increase was linked to a decrease of cases ($b_Z = -0.259$, $p_Z = 0.013$). Moreover an enhanced protective effect with increasing IR was significant in the range of around 10 °C (-1SD) ($b_Z = -0.345$, $p_Z = 0.002$) (Fig. 5-a). Interesting, this is coherent with models concerning only the 1st wave, with temperatures centered around 9.9 ± 2.4 °C, when both the T and IR resulted main predictors and their concurring positive effect was confirmed by data ($b_Z = 2.122 \div 1.461$, $p_Z < 0.001 \div 0.017$) (Fig. 5-b). This leads to the interpretation that irradiance plays a synergic protective effect at Italian typical winter temperatures, so more in cold than in warm scenarios (1st wave vs summer). Finally, while in the North of Italy IR was majorly impacting in the multi-determinant analysis, in the Centre-South two concurring models emerged, including temperature and IR separately (ΔAIC<2, lower BIC for T model), and again T resulted in a decrease of the outcome ($b_Z = -0.265$, $p_Z < 0.001$) (Table 5).

Other than IR, rH resulted to play a synergic protective effect with higher temperature, during the only 1st wave. rH was comparable in the two periods (p = 0.267) and it resulted higher in the North (p = 0.021); moreover, it was associated to an increase of the outcome in the single-determinant model for the whole sample ($b_{biv} = 0.026$, $p_{biv} = 0.033$), which is confirmed by literature [6]. However, a significant negative interaction with increasing temperatures emerges when its levels were medium-high (1SD) ($b_Z = -1.852$, $p_Z < 0.001$) (Fig. 5-c), confirming that droplets travel shorter in high-humidity environments, when atmospheric stability is higher with moderate cold weather [58], typical of the 1st wave scenario, because of slower evaporation dynamics [7]. Last researches on turbulence dynamic of puff, as the ones generated by sneezes and coughs, mainly responsible of Covid-19 transmission among individuals, just highlighted they buoyant and travel faster and longer when temperature are lower, both indoor that outdoor [59], and humidity can reasonably affect the evaporation process, so the dimension and pathway of the puff.

The inverse effect of temperature is widely found in literature [60–62]. Consistently, Harmooshi et al., 2020 [63] argued a decreased transmissibility of COVID-19 at high outdoor temperatures, and virus survival and/or droplet/aerosol evaporation also depend on the microclimatic conditions of indoor environments. However, the association between temperature and COVID-19 spread leads to controversial results, as reviewed by Pareskevis et al., 2021 [64] and by Rahimi et al., 2021 [22]. This can be due by different possible reasons. First of all, ignoring the interaction with other environmental or climatic modifier factors can produce different results, and also the effect of high outdoor temperature can be modified by the huge use of air conditioning at indoor level; finally a non-linear relationship, as the hypothesized inverse U-shape relationship [61,65], can bring to different conclusions depending on the area of the study, if tropical or temperate. It was found that temperatures increasing to about 5 °C were linked to a major transmission of the virus, while when T was higher than 5 °C transmissibility was reduced [66]. Moreover, when temperatures exceeded 20 °C, then a non-correlation was found [67], as demonstrated by the pandemic spread in most US states even in summer days with temperature above 37 °C [45]. We totally confirmed this behavior, as increasing temperatures were linked to a decrease of cases, especially with high IR, but, during the most warm period of summer, the 3d-MaxΔ+ resulted to be totally independent by temperature, suggesting some different mechanism of spread in the higher range of typical Italian summer period (about 24.5 ± 3 °C) and that warm temperatures alone cannot contain virus spread [64].

Since now, solar irradiance has been poorly investigated when controlling with the other concurring factors [68]. Our data show that solar irradiance has an important protective effect on COVID-19 spread, both through its direct role and through interaction with other determinants. Indeed, models indicate IR had an important main effect during the 1st wave, as higher levels were linked to a decrease of the outcome ($b_Z = -1.189 \div -0.763$, $p_Z < 0.001 \div 0.017$), and this impact was confirmed when considering the only Centre-South ($b_Z = -0.221$, $p_Z = 0.016$). However, other to its direct action, all the possible interaction terms were tested, obtaining interesting findings. Indeed, as previously showed, it increased the protective effect of temperature in a relatively cold range of Celsius degrees (~10 °C). Inversely, with high atmospheric stability, typically during the 1st wave and in the Northern area, high levels of irradiance acted stronger for low levels of NO_2, reasonably due for the concurring O_3 production and NO_2 filtering of solar rays from the atmosphere [42]. Coherently, it contributed to the reduction of cases when interacting with O_3 in northern area (i.e. Po Valley) and in summer, when presents a cross-over relationship, suggesting a synergic effect against the virus spread. So, it is reasonable to affirm that without considering interaction with co-factors (very often ignored in the scientific literature), the study of determinants models is probably incomplete and could bring to some controversial issues or interpretation mistakes.

The direct role of irradiance was already investigated and relies on two biological processes [13]: the first regards the well-known virucidal action of solar UV radiation, especially UV-B and UV-C, which can efficiently reduce the viral infectivity by inactivation, estimated up to 90% after 90 min of exposure for mid-latitude sites in the spring-summer months [57]. The second is linked to the synthesis of vitamin D, that is promoted by the exposure to solar UV radiation, as lead to photo-conversion of the pro-vitamin D3 in the skin [69]. Moreover, vitamin D produces a well-recognized response of the body immune system to viral and bacterial infections [70] protects pulmonary barrier, reduces inflammation. Symmetrically, D hypovitaminosis, very frequent in elderly (majorly hit by SARS-CoV-2), can enhance susceptibility to infection, as supported by studies on the association of clinical outcome and vitamin D levels [18]. Two specific issues have to be underlined in relation to our study: Italy has a latitude extension sufficient to present very different solar irradiance, with significantly greater levels e in the central-southern regions. Moreover, on a temporal scale, it was found that in Italy the irradiance is about 10-fold higher during summer than in winter and, consequently, blood sampling showed the minimum level of vitamin D in April and maximum in September [71]. Both aspects are well-fitting the early phase of Covid-19 pandemic and our most convincing result on the importance of irradiance is its crucial association when data of the only 1st wave were studied. The very heterogeneous levels of irradiance, present in Italy during the national lockdown of the 1st wave, allows to impute a protective effect of the solar power on the population, that was less prone to manifest infection in the southern part of the country as well as in summer, reasonably enhanced by the possible concurring action of ozone. Indeed, the unknown mixing effect on infection decrease in summer, given by lock-down policy of preceding months and very different environmental conditions (in terms of both air pollution and climate), can act in the same direction but with unwell defined weights. However, freezing the data at the only summer period and studying the variability of the only summer outcome, even notably reduced respect to the 1st wave, undoubtedly shows that environment pollution loses its importance, probably because of the significantly lower concentrations of PM and NO_2, while IR and O_3 were protective only if both presented high levels (Fig. 4-d). So, in summer, the interrelation among persons, represented by population size, but also, with less extent, by the vehicular mobility, are the parameters that mainly account for.

Wind speed resulted a significant contributor to the decrease of the outcome overall and during the 1st wave ($b_{biv} = -0.292 \div$-0.294, $p_{biv} = 0.009 \div 0.044$). During the 1st wave it remained significant also in multi-determinant model ($b_Z = -0.138 \div 0.142$; $p_Z = 0.029 \div 0.040$), as its presence has a major impact in ambient air cleaning and virus droplets dispersion during the major atmospheric stability period, other that the reduction of pollutants than are hypothesized to favor infections. This was also the interpretation of previous works [5,62,68] linking the low atmospheric stability to the dispersion and dilution of the air pollutants ($PM_{2.5}$ and NO_2), positively correlated with the peak of COVID- 19 cases on a 14-days lag basis.

In summary, our study has the strength to identify the demographic, climatic, and pollution-related determinants of Covid-19 spread, which hit northern Italy more dramatically than the remaining part of the nation during the first wave. Similarly, it addresses the reasons behind the drastic reduction of infections in summer and suggests interpretation of the determinants resulting from the statistical analysis. Moreover, the applied statistics approach is tailored on the specific study design, as it allows to investigate the factors of greatest impact on a single dependent variable, when considering repeated measures with a hierarchical structure.

The main drawback of the study is the intrinsic limitation of the ecological study design, useful to generate hypotheses but not to verify them [12] and the use of ambient data. Much more attention should be given to indoor environments, where transmission usually occurs [10], but it is practically unfeasible to collect quantitative information on indoor air pollutants and microclimate on a national scale, or even estimate accurately their variability. Thus, the outdoor data used here must be considered as surrogates of indoor data and actual human exposures because of the well-known influence of outdoor pollution on indoor air quality [72] (infiltration processes) and meteorological conditions on indoor microclimate. Another critical point was the choice of the (14–20)-lag period [45], that was supposed the same for all the variables. However, such a choice was supported by other studies [5, 6, 13, 21]. Moreover, in the non-lockdown summer period scenario, contagions were probably affected by specific social context (concerts, events etc.), ignored in the study. Data have been aggregated on provincial level, allowing a discretization of the analysis on a national level. An advantage of the chosen statistical approach is that it accounts for regional-specific variability, as the heterogeneous testing capacity across regions. Moreover, the selected outcome is independent on subject specific characteristic (social, economic, health-related) as it represents a picture of the scenario retrospectively linked to the moment of the 3d-Max$\Delta+$. Another important strength of our study is that interactions among covariates were tested, revealing the crucial synergic action of solar irradiance with T, NO_2 and O_3.

4. Conclusions

In conclusion, the spread of SARS-CoV-19 is linked to a very tangle mesh of causes and all the studies proposed by the international scientific community can add a peace to the whole puzzle. As a contribute to this, the key point of our study is that people interrelationship remains an important risk management option in pandemic control, as the population size impact on the outcome in all the considered scenarios. High population size and density can be considered a proxy of different aspects: large cities are usually provided by good interconnections as highways and airports, favoring mixing of people from different areas [24]. Moreover, important drivers of the epidemic as schools and universities are majorly present in areas of high population density and healthcare systems can be more efficient in cities than in remote areas, thus favoring the easiest performing of diagnostic swabs [17,73]. Despite affected by policy measures and socio-economic and cultural aspects, distancing of people, test-and-trace and self-quarantine remain effective tools in control of pandemics [17]. As Covid-19 transmission predominantly occurs in indoor environments, prevention and protection strategies remain crucial, such as physical distancing, face masks, proper air-conditioning/ventilation systems, or less common options as the use of air purifiers or IAQ monitors [15].

Even if our analysis does not allow inferring causality, the correlation of infection spread with NO_2 and $PM_{2.5}$ levels suggests the importance of air pollution control to prevent its deleterious effect on Covid-19 susceptibility. The meteorological aspects, especially linked to higher temperatures and irradiance, strongly interacting with both NO_2 and O_3, address the importance of area-specific studies. In particular, especially in areas with low irradiance and high pollution, it can suggest the benefit of integration of Vitamin D to population, as widely confirmed and reviewed [18].

Moreover, considering the short-term effect of widely used mRNA vaccination doses [74], these results can address to schedule the vaccination campaign nearly before the contagious-prone period of the year. Finally, a study methodology that allows considering the different concurring factors together, including their possible interactions, is more reliable in representing the correct picture of the virus spread scenario, and preserve from drawing false or controversial conclusions. The synergic actions can so explain some different results of ecological studies, because of site-specific combinations in the effect of concurring factors, whether climatic, demographic or environmental.

Author contribution statement

Patrizia Urso: conceived and designed the experiments, analyzed and interpreted the data, wrote the paper; Andrea Cattaneo: analyzed and interpreted the data, wrote the paper; Salvatore Pulvirenti: contributed reagents, materials, analysis tools or data; Franco Vercelli: contributed reagents, materials, analysis tools or data; Domenico M Cavallo: analyzed and interpreted the data, wrote the paper; Paolo Carrer: analyzed and interpreted the data, wrote the paper.

Data availability statement

All data analyzed during this study are included in this published article in its supplementary information files, excluding data of solar irradiance. The data of solar irradiance of this study are available from Italian Military Airforce (COMET) but restrictions apply to the availability of these data, which were used under permission for the current study, and so are not publicly available.

Declaration of interest's statement

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15358.

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