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Effects of environmental parameters and their interactions on the spreading of SARS-CoV-2 in North Italy under different social restrictions. A new approach based on multivariate analysis.

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14 **Keywords**

15 SARS-CoV-2, COVID-19, temperature, solar radiation, particulate matter, relative humidity, hospitalization,
16 chemometrics

17

18 **Abstract**

19 In 2020 North Italy suffered the SARS-CoV-2-related pandemic with a high number of deaths and hospitalization. The
20 effect of atmospheric parameters on the amount of hospital admissions (temperature, solar radiation, particulate
21 matter, relative humidity and wind speed) is studied through about 8 months (May-December). Two periods are
22 considered depending on different conditions: a) low incidence of COVID-19 and very few regulations concerning
23 personal mobility and protection ("free/summer period"); b) increasing incidence of disease, social restrictions and
24 use of personal protections ("confined/autumn period"). The "hospitalized people in medical area wards/100000
25 residents" was used as a reliable measure of COVID-19 spreading and load on the sanitary system. We developed a
26 chemometric approach (multiple linear regression analysis) using the daily incidence of hospitalizations as a function
27 of the single independent variables and of their products (interactions). Eight administrative domains were considered
28 (altogether 26 million inhabitants) to account for relatively homogeneous territorial and social conditions.
29 The obtained models very significantly match the daily variation of hospitalizations, during the two periods. Under the
30 confined/autumn period, the effect of non-pharmacologic measures (social distances, personal protection, etc.)
31 possibly attenuates the virus diffusion despite environmental factors. On the contrary, in the free/summer conditions
32 the effects of atmospheric parameters are very significant through all the areas. Particulate matter matches the
33 growth of hospitalizations in areas with low chronic particulate pollution. Fewer hospitalizations strongly correspond
34 to higher temperature and solar radiation. Relative humidity plays the same role, but with a lesser extent. The
35 interaction between solar radiation and high temperature is also highly significant and represents surprising evidence.
36 The solar radiation alone and combined with high temperature exert an anti-SARS-CoV-2 effect, via both the direct
37 inactivation of virions and the stimulation of vitamin D synthesis, improving immune system function.
38

39 **1. Introduction**

40 At the end of 2019 a novel coronavirus, now defined as SARS-CoV-2, has emerged in Wuhan (China) and it has rapidly
41 spread worldwide, becoming a very serious health concern (Lu et al., 2020). Its related disease, known as COVID-19,
42 has caused more than 5 million deaths across the globe (WHO, 2021a). This pathogen is an enveloped non-segmented
43 RNA virus with a spherical-shape (Xu et al., 2020). Other RNA viruses show some potential pathogenetic mechanisms
44 and clinical manifestations similar to SARS-CoV-2, thus many studies have focused on researching possible similarities
45 among these pathogens and have considered that the spreading of this new pandemic may be associated with
46 seasonal and environmental factors (Fiorino et al., 2021b). After China, North Italy was one of the most impacted
47 areas by the epidemic in the world since its beginning. However, its incidence has not resulted homogeneous across
48 distinct regions and areas in this nation as well as depending on the different seasons and climatic conditions
49 (Quaranta et al., 2020). These observations have led researchers to accurately consider
50 physical/environmental/meteorological parameters (among others) as factors able to control the diffusion and the
51 severity of the disease caused by SARS-CoV-2 infection (Lolli et al., 2020). This approach derives from the observation
52 that other well-known respiratory viruses display seasonal fluctuations of their epidemic manifestations, with distinct
53 peak incidence (Nichols et al., 2008; Moriyama et al., 2020). It is well-known that both outdoor and indoor distinct
54 climate conditions and environmental factors have an important impact on the transmission efficiency of these
55 pathogens as well as on the human susceptibility to them (Leung, 2021). Temperature, solar radiation, particulate
56 matter, relative humidity, and wind speed have been identified as factors capable to influence the replicative fitness,
57 transmissibility, and the pathogenicity of respiratory viruses as well as the severity of the infectious diseases caused by
58 these pathogens. The above-mentioned climate- or ambient-conditions may act both by altering the survival and
59 spread of viruses in the environment and by changing host's susceptibility against them (Moriyama et al., 2020; Audi
60 et al., 2020). Only a few studies have examined the relationship between wind speed and the development of
61 respiratory tract diseases, although no definitive conclusions have been reached, whereas no reports concerning the
62 effects of wind speed on the immune system activities are currently available (Toczyłowski et al., 2021). Furthermore,
63 in a large social community, the meteorological conditions must be considered together with personal mobility and
64 with the progressive restrictions adopted during the course of the pandemic, making more complex the interaction
65 between climate, environment, and health. Moreover, the effect of atmospheric parameters could vary according to
66 the mutual relationship among them.

67 The aim of our study was to better understand what factors may influence the transmissibility of SARS-CoV-2 in terms
68 of hospital admission. Three main features distinguish our approach respect to many other works published on this
69 subject: a) we considered the daily variation of factors within single administrative areas instead of comparing
70 different zones; such a condition is more realistic, assuming that people doesn't move through different provinces to
71 prevent the viral infection; moreover, other confounding factors (for instance the demographic variables) are not
72 applicable within a single area; b) multivariate statistical models were used considering both single environmental
73 parameters (single variables) as well as their interactions: this chemometric approach has never been used in this
74 context up today and give rise to new findings; c) the effect of non-pharmacologic measures (social distances,
75 personal protection, etc.) is considered by modelling two different time periods: one free of mobility and social
76 restrictions (18 May – 6 November 2020), the other characterized by progressive and differentiated social limitations
77 established during the local "second wave" (14 November – 31 December 2020). The study focuses on North Italy,
78 because of its high incidence of the COVID-19 and as a representative area of the western countries for its socio-
79 economic features (Postiglione et al., 2020; Rosano et al., 2020).

80

81 **1.1 Effects of temperature, UV radiation, humidity, particulate matter, and wind speed**

82 Atmospheric parameters can have a crucial impact on the pandemic crisis by several routes, at least three points can
83 be considered: the direct effect on the virus survival, the interaction with the media necessary for the diffusion of the
84 virions from person to person (for instance the droplets stability) and the effect on the human immune system. In
85 open-air conditions all these features interact with each other, so it is possible that ecological studies highlight
86 controversial roles of the atmospheric parameter in different areas or under different conditions; recent reviews show
87 several of these unusual cases all over the world (Jayaweera et al., 2020; Paraskevis et al 2021; Srivastava, 2021), but
88 the subject is already well known for respiratory viruses (Pica and Bouvier, 2012).

89

90 *1.1.1 Effect of atmospheric parameters on the human immune system*

91 It has been shown that atmospheric factors may affect and also alter the normal function of several defense
92 mechanisms in humans. In the course of viral infections, the first line of protection is provided by the respiratory
93 mucosal barrier. It consists of three main elements, including: the mucus layer, the surface liquid layer and the cilia on
94 the surface of the bronchus epithelia. All these elements cooperate in counteracting invading pathogens by promoting
95 their mucociliary clearance (Kudo et al., 2019). Nevertheless, if the virus bypasses this defense mechanism, further

96 protective responses are activated, and innate and adaptive arms of the host's immune system are triggered. Viral
97 pathogen-associated molecular patterns (PAMPs) are recognized by Toll-Like Receptors on the membrane of antigen-
98 presenting cells, leading to the activation of type-I interferons (IFNs) and to the transcription of a large spectrum of
99 IFNs-regulated genes as well as to the stimulation of specific T- and B-cells. Some experimental studies have shown
100 that low humidity conditions and dry air in the environment cause a higher susceptibility to some viruses, such as
101 influenza viruses in humans, via an impairment in the function of the muco-ciliar barrier as well as in the activity of
102 innate immunity (Shephard and Shek, 1998; Eccles, 2002; Kudo et al., 2019). Furthermore, some researchers have
103 suggested that both environmental- as well as host's body temperature may affect both innate and adaptive immune-
104 mediated antiviral responses in animals and humans, but, to date, the results of the available investigations are not
105 univocal. In a model of guinea pigs, investigating the factors involved in influenza virus transmission, animals housed
106 at 5° C presented a higher viral transmission in comparison with ones housed at 20° C and 30° C, but innate responses
107 were comparable between the three different groups of animals (Lowen et al., 2007). On the other hand, a study in
108 mice has shown that elevated environmental temperature (36° C) may impair adaptive immune responses to influenza
109 A virus infection (Moriyama and Ichinohe, 2019). Furthermore, also the host's body temperature may influence innate
110 and adaptive immune response. One research has suggested that warm temperature in mouse airway cells may
111 improve innate defense against the common cold virus, decreasing its replication capability; however, the better
112 antiviral effect may be detectable with a restricted range of temperature (35-37° C) (Foxman et al., 2015). Exposure to
113 particulate matter causes cell and mitochondrial damage in mammalian and human tissues. This event is associated
114 with the generation of reactive oxygen species (ROS). The synthesis and release of these mediators mainly occurs
115 during the phagocytosis of the pollutant particles by macrophages and by antigen-presenting cells. Furthermore, the
116 usual production of ROS is up-regulated in mitochondria, following pollutants-mediated injury. The increase in the
117 release of these free radicals triggers the onset/exacerbation of inflammatory events, leading to the release of
118 cytokines, interleukins, and mediators and to the generation of a phlogistic microenvironment (Valacchi et al., 2020).
119 Experimental "in vitro" studies have shown that the exposure of human peripheral blood mononuclear cells to metal-
120 containing particulate matter shifts the balance of Th1/Th2 and Treg/Th17 lymphocyte, promoting the polarization of
121 T cells towards Th1 and Th17 subsets. Th1 and Th17 cells induce the release of IFN- γ and IL-17. These mediators
122 down-regulate the expression of FoxP3 protein, promoting the inhibition of T reg cells and stimulating pro-
123 inflammatory activity of Th17 lymphocytes. These events lead to an exacerbation of tissue inflammation (Gałuszka et
124 al., 2020; Matthews et al., 2016). It is well-known that sunlight prevents respiratory tract infection mediated by

several viruses, such as the influenza virus (Walker and Ko, 2007; Tseng and Li, 2005). Exposure to solar radiation also affects the survival of several pathogens, exerting germicidal and antiviral activities. Current evidence suggests UV-B rays are effective in inactivating respiratory viruses via the induction of irreversible modifications in their nucleic acids or proteins (Ianevski et al., 2019) and in inducing the activation of vitamin D (VD) in the human skin. Some epidemiological and clinical studies suggest that this fat-soluble compound exerts important effects in counteracting respiratory tract viruses-mediated infections (Hughes and Norton, 2009). A relationship between vitamin D deficiency and a higher risk of intensive care admission (Remmelts et al., 2012) as well as more elevated mortality rates in subjects with more severe forms of pneumonia has been demonstrated since several years ago (Dancer et al., 2015). However, despite the protective role of VD has been reported, the prevalence of low vitamin D status is still a health problem worldwide, involving not only the oldest individuals but also all age classes and people living in geographical areas with sun exposure all year round (Holick and Chen, 2008; Hughes and Norton, 2009; Palacios and Gonzales, 2014). VD, alone or in cooperation with other micronutrients, improves the function of the innate and adaptive arm of the immune system. In particular, this fat-soluble compound prevents an excessive inflammatory response, by down-regulating the activity of some pro-inflammatory cytokines, such as IL-6, IL-8, IL-12, IFN- γ , and Th17 and Th1 lymphocytes, and promoting the up-regulation of T regulatory cells. This activity results in the modulation and control of immune response strength (Chang et al., 2010; Kim et al., 2020).

141

1.1.2 Laboratory studies and simulations

More firm indications arise from laboratory studies that have tested the effect of temperature on the survival of SARS-CoV-2 (Chin et al., 2020; Matson et al., 2020; Riddell et al., 2020) and also other DNA and RNA viruses (HBV, HCV, and HIV) under controlled conditions (Than et al., 2019; Doerrbecker et al., 2011; Paintsil et al., 2014; Song et al., 2010). A large series of reviews concerning in-vitro data about several coronavirus types (Aboubakr et al., 2020; Guillier et al., 2020), show that the increase of temperature reduces the viability of these pathogens (including SARS-CoV-2) on different materials in a similar way. A mathematical model has been developed, but the uncertainty in predicting the inactivation of any coronavirus strains, belonging to Alphacoronavirus and Betacoronavirus genera on different materials as a function of temperature, persists (Guillier et al., 2020). Furthermore, it is now well-known that solar radiation, especially the UV-B component (315-280 nm), counteracts the survival of SARS-CoV-2 (Ratnesar-Shumate et al., 2020). On the other hand, the UV-C component (< 280 nm) is unable to get the ground and is absorbed by the atmosphere, however, it is commonly used as a germicidal tool against viral

154 particles (Walker and Ko, 2007). Theoretical computations based on laboratory results indicate that the dose of UV-B
155 solar radiation reaching the Earth's surface is effective for the control of the SARS-CoV-2 diffusion (Sagripanti and
156 Lytle, 2020; Nicastro et al., 2020). The UV-A (400-315 nm) channel has not a direct activity against SARS-CoV-2 (Darnell
157 et al., 2004), but it may exert some benefits towards this pathogen, as the UV-A radiation induces cardiovascular and
158 metabolic protective effects upon photo-release of nitric oxide from stores in the skin (Cherrie et al., 2021).
159 High values of air relative humidity are considered an effective inhibitory factor for SARS-CoV-2 (Chan et al., 2011),
160 MERS-CoV (van Doremalen et al., 2013), SARS-CoV (Casanova et al., 2010), and Influenza A (Yang and Marr, 2011).
161 Also, Campos et al. (2020) have reported that the SARS-CoV-2 is reduced by heating more efficiently when the relative
162 humidity is higher, in agreement with other RNA viruses. Nevertheless, the increase of environmental relative
163 humidity is less effective in promoting the inactivation of coronaviruses in both solid and liquid fomites in comparison
164 with temperature. In particular, the data collected by Guillier et al. (2020) show that the plot describing relative
165 humidity and the reduction of virus infectivity is extremely variable, and at >99% relative humidity the virus infectivity
166 is unpredictable and any relationship between these parameters is lost. A specific study highlights that both high
167 (>85%) and low (<60%) relative humidity determines a significant decrease of infectivity in models of influenza virus
168 and SARS-CoV (Prussin et al., 2018), substantially in agreement with the review by Moriyama et al. (2020). The
169 researchers have observed that in droplets the inactivation of influenza viruses occurs at intermediate relative
170 humidity (40% to 60%). The review by Ahlawat et al. (2020) has concluded that in indoor environment the chances of
171 airborne transmission of SARS-CoV-2 are higher in dry conditions (<40% relative humidity) than those detectable in
172 humid places (> 90%).
173 The relationship between the effect of water vapour on the stability of SARS-CoV-2 and on the stability of droplets is
174 still to be defined: apparently, the pathogen suffers the complete dryness, in agreement with its reduced transmission
175 in dry climates, whereas the same effect in wet environments contradicts this hypothesis (Corpet, 2021); also, it must
176 be considered that the droplets enlarge and fall down if humidity is high enough (Jayaweera et al., 2020). The virus
177 diffusion after sneezing calculated at 5°C and 20°C and at 50% and 90% relative humidity shows that the infection risk
178 distance is less than 1.75 m at 5°C and slightly more than 1.75 m at 20°C. This effect is due to the balance between the
179 stability of droplets which represent the most infectious media (liquid) and the dispersion of evaporation nuclei which
180 may remain infectious for a considerable amount of time, travelling long distances (Wang et al., 2021).
181 Another atmospheric parameter that is considered very critical for the COVID-19 diffusion and severity is the
182 particulate matter (PM). Genetic material from the SARS-CoV-2 virus was detected on particulate matter less than 10

183 μm (PM10) in the city of Bergamo (Italy), severely impacted by SARS-CoV-2 infection (Setti, et al., 2020). Other data on
184 Italian areas during the same COVID-19 crisis (Chirizzi et al., 2020) show that in crowded sites the PM10 results in a
185 vector for SARS-CoV-2, whereas in different contexts the particulate resulted negative. In Madrid, no presence of
186 SARS-CoV-2 was detected in particulate matter of various sizes (10, 2.5, and 0.1 microns) during a period with a
187 relatively reduced circulation of the coronavirus, low PM concentration, and high temperature (Linillos-Pradillo et al.,
188 2021). Very similar results have been reported from the Padova province (North Italy), in the earliest phases of the
189 pandemic diffusion in that area (Pivato et al., 2021). Theoretically, the SARS-CoV-2 can persist on the particulate
190 surfaces and this event may contribute to its transmission (Duval et al., 2021). Particulate materials may serve as a
191 shuttle for the virions, but this aspect cannot be generalized, as the characteristics of particles surfaces are variable
192 and several features of the virions-particle interaction can decrease the virus viability (Wathore et al., 2020; Nieto-
193 Juarez and Kohn, 2013). The environmental and meteorological conditions may eventually exert additional effects
194 (positive or negative) on the virus transmissibility (for instance humidity, UV irradiation, evaporation due to
195 temperature or wind).

196 The effect of air movements on SARS-CoV-2 is difficult to measure, but simulations can help in deciphering the effect
197 of wind alone. Li et al. (2020) have computed that the larger droplets (ranging from 100 to 1000 μm) increase their
198 travel distance with the wind speed, taking into account also the evaporation rate at specific values of temperature
199 and relative humidity. Similar conclusions are reported also for smaller droplets (10 – 100 μm) and, even if at high
200 wind speed (3m/s) the human thermal plume is destroyed, their deposition on a susceptible person downwind is ten
201 times higher than at low speed (0.2m/s; Yang et al., 2021). Under such a condition (downwind), the wind speed may
202 be a major infection factor as it narrows the infectious plume and relatively-high virion concentrations can be found
203 even at 9 m away from the infective person, at least under the studied conditions (wind speed 0.1 to 11.5 m/s; Rezaali
204 and Fouladi-Fard, 2021).

205

206 *1.1.3 Ecological studies - global considerations*

207 In addition to the indications about the effects of a single parameter obtained by laboratory data or by simulations, a
208 lot of ecological studies have investigated the association between meteorological and environmental conditions, the
209 spread of the pandemic, and its severity. It is very difficult to compare these researches because they consider
210 different areas, time periods, and parameters (for instance the temperature or the daily temperature excursion).
211 Nevertheless, general reviews performed on the global scale or on continental or sub-continental areas tried to

212 identify systematic relationships among the COVID-19 and environmental parameters. The results are often
213 contradictory, but the efficacy of higher temperatures in preventing virus diffusion seems one of the few common
214 features in all studies over the world (Kubota et al., 2020; Ma et al., 2020; Wu et al., 2020a; Asher et al., 2021;
215 Grespan et al., 2021; Sanchez-Lorenzo et al 2021; Srivastava, 2021; Notari, 2021), even if different results are reported
216 for the first wave of the pandemic, up to spring 2020 (Sfica et al., 2020; Paraskevis et al., 2021).

217 Higher temperatures are commonly associated to higher solar radiation on a global scale, and the effect of the UV-B in
218 slowing the diffusion of SARS-CoV-2 may be observed (Nicastro et al., 2020; Asher et al., 2021; Grespan et al., 2021;
219 Srivastava, 2021; Tang et al., 2021). A possible confounding factor associated with the temperature and solar radiation
220 anomalies is explicitly mentioned by Sfica et al. (2020) and by Byass (2020). The latter researcher has studied
221 approximately 18000 cases of COVID-19 in China and has reached the following conclusion: although UV radiation is
222 considered effective in counteracting virus survival, sunshine days induce a higher sociality and accordingly a higher
223 probability of transmission.

224 The effect of air relative humidity on the SARS-CoV-2 diffusion has been considered by several authors and
225 contradictory results have been described (Paraskevis et al., 2021). Some studies, enrolling large population cohorts,
226 have detected no significant relationship with the pandemic (Asher et al., 2021; Grespan et al., 2021), whereas others
227 have observed a protective effect (Gupta et al., 2020; Wu et al., 2020a; Ma et al., 2020, Srivastava, 2021), but also
228 positive correlations with the COVID-19 diffusion have been observed (Gupta et al., 2020; Suhaimi et al., 2020). A
229 preliminary evaluation of most impacted cities in Brazil during spring suggests that intermediate relative humidity
230 (about 80%) favours the transmission rate (Auler et al., 2020). Further controversy is whether to consider humidity in
231 relative or absolute terms. For instance, low absolute humidity ($4\text{--}7\text{ g/m}^3$ humid air) and specific humidity ($3\text{--}6\text{ g/kg}$
232 dry air) characterize the areas in the world, suffering a high spread of SARS-CoV-2. On the other hand, the relative
233 humidity values of the same affected areas do not allow the identification of the poorly-affected territories by the
234 pathogen in the northern hemisphere (Sajadi et al., 2020).

235 Further studies have shown that air pollution also is able to affect the transmission of SARS-CoV-2 (Wu et al., 2020b;
236 Maleki et al., 2021; Pansini and Fornacca, 2021; Srivastava, 2021; Travaglio et al., 2021, among others). However, it
237 remains unclear what is the pathogenetic role of particulate matter in humans, as it may act as a carrier for the virus,
238 it may induce an acute inflammatory response in the respiratory system or it may cause a chronic injury in organs and
239 tissues, persistently exposed to air pollutants (Comunian et al., 2020).

240 In general wind speed is not considered a major factor in SARS-CoV-2 spreading. Only a few studies have investigated
241 the effects of this parameter in the transmission of the virus (Srivastava, 2021). In the review by Asher et al. (2021),
242 this factor has been recognized as a protective agent (the higher the wind speed, the lower the deaths for COVID-19),
243 in agreement with studies in Brazil (Rosario et al., 2020) and Iran (Ahmadi et al., 2020). However, no beneficial roles of
244 this ambient parameter have been demonstrated in further studies (Gupta et al., 2020).

245

246 **2. Materials and methods**

247 **2.1 Epidemiological and demographic data**

248 In Italy, epidemiological data are available on daily basis since the 24th February 2020, from national authorities
249 (<https://github.com/pcm-dpc/COVID-19>), in particular, the daily number of new cases should represent a possible
250 measure of the pandemic spread, but unfortunately, it is not completely reliable (Sartor et al., 2020), as the number of
251 daily tests changes strongly according to the administrative territory, day of the week (lower number of tests on
252 Saturday and Sunday) and time since the beginning of the pandemic. So, the interpretation of the results available
253 presents some problems and data are not comparable considering different administrative areas; moreover, it
254 strongly depends on the efficacy of the contact-tracing survey, that during the strongest pandemic rate was not
255 sufficient in identifying all the contagious persons (Pezzutto et al., 2021). It must also be considered that the contact-
256 tracing cannot be done for asymptomatic individuals, who are not intercepted by screening tests. It is likely that a
257 significant number of cases has been excluded, as about 43% of infected subjects were asymptomatic in February-
258 March 2020 according to a whole-population screening performed in the Vo' Euganeo village, in Regione Veneto
259 (Lavezzo et al., 2020). For these reasons the prevalence of hospitalized people in medical area wards on 100000
260 residents (RCS) was used to account for the spread and incidence of the pandemic. This parameter was considered, as
261 the criteria for patient hospitalization are more homogeneous, accurately counted, and ensure adequate numerosity;
262 the Intensive Care Units cases were excluded because of lower numerosity and more severe clinical status of patients,
263 non-reflecting the general health situation (Struyf et al., 2021; Lorenzoni et al., 2020). The number of hospitalized
264 cases is available for regional administrations and autonomous provinces. In our study we have considered eight
265 areas, that are contiguous and cover the physiographic area between the Alps (in the Northern border) and the
266 Apennines (in the South): Val d'Aosta, Piemonte, Lombardia, Provincia autonoma di Trento (later on simply Trento),
267 Provincia autonoma di Bolzano (later on simply Bolzano), Veneto, Friuli Venezia Giulia, Emilia-Romagna (Fig.1). More

268 than 26 million people live in these areas, confirmed positive cases were 1210752 at the 31st December 2020, hospital
269 occupancies (excluding intensive care units) 2367162, 51024 deaths.
270 Demographic data referred to the 2019 are taken from the national repository
271 (http://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES1).
272

273 **2.2 Atmospheric parameters**

274 In order to get homogeneous data on daily basis over the study area, the databases from Copernicus data sets
275 (<https://climate.copernicus.eu/>) were used for collecting the following data:

- 276 • temperature (labelled T, ERA5 hourly data on single levels from 1979 to present, average 2m temperature at
277 12.00 and 24.00, recalculated as °C, [https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-](https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-single-levels?tab=form)
278 [single-levels?tab=form](https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-single-levels?tab=form)),
- 279 • UV solar radiation (labelled S, ERA5 hourly data on single levels from 1979 to present, sum of mean surface
280 downward short-wave radiation flux at 8.00, 12.00 and 16.00, W/m²,
281 <https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-single-levels?tab=form>),
- 282 • particulate matter less than 2.5µm (labelled P, CAMS daily air quality analyses and forecasts for Europe,
283 concentration at 12.00, recalculated as µg/m³,
284 <https://ads.atmosphere.copernicus.eu/cdsapp#!/dataset/cams-europe-air-quality-forecasts?tab=form>),
- 285 • relative humidity (labelled H, ERA5 hourly data on pressure levels from 1979 to present, average at 8.00,
286 12.00 and 16.00, percentage, [https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-pressure-](https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-pressure-levels?tab=form)
287 [levels?tab=form](https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-pressure-levels?tab=form)),
- 288 • wind (labelled W, ERA5 hourly data on single levels from 1979 to present, module of the eastward
289 component of the 10m wind, maximum velocity at 08:00, 14:00 or 20:00, m/s,
290 <https://cds.climate.copernicus.eu/cdsapp#!/dataset/reanalysis-era5-single-levels?tab=form>).

291 To compare regional sanitary data with atmospheric ones, the weighted average of T, S, P, H and W was calculated on
292 regional basis by measuring the parameters of the main provincial localities and using the provincial inhabitants as
293 weight. This calculation was adopted because in the study area most people live in urban zones (91%; according to the
294 last Italian General Census, available for the 2011 at <https://www.istat.it/it/archivio/104317>).
295

296 **2.3 Searching for delay from environmental stress to hospitalization**

297 A multiple linear regression analysis has been performed to create multivariate models, considering the RCS as
 298 dependent variable (response) and the atmospheric parameters T, S, P, H, and W (rescaled from 0 to 1, as indicated in
 299 Brereton, 2007) as independent variables; moreover, not only the single independent variables were taken as factors,
 300 but also and products between independent variables were used as factors in the multivariate models: T·S, T·P, T·H,
 301 T·W, S·P, S·H, S·W, P·H, P·W, and H·W. This means that the general function relevant to the multivariate models has
 302 the following form:

$$303 \text{ RCS} = f(\text{factor1}, \dots, \text{factor 15}) = f(T, S, P, H, W, T \cdot S, T \cdot P, T \cdot H, T \cdot W, S \cdot P, S \cdot H, S \cdot W, P \cdot H, P \cdot W, H \cdot W)$$

304 The mathematical form of the function f can be found using the well-known regression procedure.

305 The Solver routine of Microsoft Excel was used for the calculation; the standard deviation of regression (square root of
 306 the sum of square distances between RCS and the computed model, divided by the number of degrees of freedom), as
 307 the minimizing parameter; this is the Multiple Linear Regression approach (MLR) (Brereton, 2007). An initial analysis
 308 using the atmospheric parameters alone (T, S, P, H, and W) produced standard deviations systematically worse than
 309 including also the interactions (Fig.S1), so this simpler approach was no longer developed. We have used the concept
 310 of lag time, defined as the time period between atmospheric stress and hospitalization (Haghshenas et al., 2020). This
 311 variable represents an indication of how the computed model is realistic, as the lag interval should include both the
 312 incubation time and other possible causes of delay in the appearance of the symptoms and of the overt disease.
 313 We checked for the best lag time ranging from 8 to 24 days (Fig. S1) and the lag time corresponding to the best fit was
 314 used for the multivariate analysis.

315

316 **2.4 Multivariate analysis**

317 Several atmospheric parameters (independent variables) have been considered: temperature (T), solar radiation (S),
 318 particulate matter (P), relative humidity (H), and wind speed (W). The chosen chemometric approach consists in
 319 writing equations (statistical models) in which the dependent variable (response) is a function of single independent
 320 variables and of their products two at a time (interactions):

$$321 \text{ RCS} = b_0 + b_1 T + b_2 S + b_3 P + b_4 H + b_5 W + \\ 322 + b_6 T \cdot S + b_7 T \cdot P + b_8 T \cdot H + b_9 T \cdot W + b_{10} S \cdot P + b_{11} S \cdot H + b_{12} S \cdot W + b_{13} P \cdot H + b_{14} P \cdot W + b_{15} H \cdot W \quad (\text{eq. 1})$$

323 Single variables and interactions are called factors. In this case, the number of degrees of freedom is calculated as the
 324 difference between the number of observations and the numbers of regression coefficients in eq. 1, which are 16 (b_i , i
 325 = 0, ..., 15).

326 As a dependent variable (response) we used the hospitalized people in general medical wards on 100000 residents
327 (labelled as RCS).
328 In fact, the classical statistical methods adopt a univariate approach considering one independent variable at a time; in
329 this univariate approach, for each variable, the mean and standard deviation are used, and an equation putting the
330 response as a function of the single variable is studied as a possible univariate statistical model. However, the
331 univariate approach is very limited, because it cannot show correlations among all the variables capable of influencing
332 the response; besides correlation, also interactions between independent variables do emerge: this means that one
333 can understand whether the *simultaneous changes* of variables are capable of influencing the response. On the
334 contrary, when the multivariate approach is adopted, it becomes possible to evaluate correlations, interactions and
335 also to evaluate the relative influence of all the factors (single variables and products) on the response: this is
336 performed by evaluating the significance of the regression coefficients (b_0, \dots, b_{15} in eq. 1) and their numerical values
337 (opportunately scaled).

338

339 2.4.1 MLR

340 The multivariate models corresponding to eq. 1 are created by the MLR method.

341 MLR is the multivariate extension of the univariate Ordinary Least Squares (OLS) method: in OLS the independent
342 variable is a vector ($n \times 1$, meaning n lines and 1 column), while in MLR the m factors are m columns in the $n \times m$
343 matrix (\mathbf{X}) representing the starting dataset. The response y is a vector ($n \times 1$) both for OLS and MLR. The equation of
344 the model is:

$$345 \quad \mathbf{y} = \mathbf{X} \mathbf{b} \quad (\text{eq. 2})$$

346 where \mathbf{b} is the vector of the regression coefficients. When also the constant value b_0 (intercept) is computed in eq. 1,
347 the number of regression coefficients is $m' = m + 1$ and the dimension of the vector \mathbf{b} is $m' \times 1$, while the matrix \mathbf{X}
348 becomes $n \times m'$ and its first column is made of unitary values.

349 The advantages of MLR with respect to OLS are great. By MLR it is possible to evaluate: all the possible correlations
350 and the interactions among all the variables; the relevance of variables in influencing the response; the relative
351 importance of variables; the *predictive ability* of the model. The capability of a MLR model to predict unknown
352 samples can be evaluated by a simple chemometric tool: Cross Validation (CV). The power of CV lays in the fact that it
353 does not need standard samples: this is perfect in a situation where standards do not exist, like the case of the present
354 work. The CV method simply works by calculating the distance of each sample from the model created by all the other

355 samples, and then calculating the statistical mean of all the obtained distances: square root of the ratio between the
 356 summation of the distances and the degrees of freedom of the model ($n-m'$), called Root Mean Square Error in CV
 357 (RMSE_{CV}). In order to have models highly performing in prediction, RMSECV must tend towards zero.
 358 Once a MLR model is created, the validity of the equation must be verified by an ANOVA test (Analysis Of VAriance):
 359 the variability due to the model (MSS, Model Sum of Squares, m degrees of freedom) must be much higher than the
 360 variability due to uncertainty (RSS; Residual Sum of Squares, $n-m'$ degrees of freedom). Consequently, the Fisher
 361 coefficient F obtained as the ratio between MSS/m and $RSS/(n-m')$ must be much higher than 1: the corresponding p -
 362 value (p) of F -test should be very low.
 363 After passing the ANOVA test, some figures of merit must be evaluated: the correlation coefficient R , RMSE, and the
 364 corresponding values in prediction mode (R_{CV} and RMSE_{CV}). The coefficient R quantifies the correlation between the
 365 response and the independent variables, while RMSE quantifies the mean distance between the experimental y values
 366 and the relevant values re-calculated by the model. These figures of merit can be calculated by creating the response
 367 plot, in which the recalculated values of y are plotted versus the experimental values of y ; in this plot, the target line
 368 has null intercept and unitary slope.
 369 As for the relative relevance of variables, it is estimated through the numerical values of the relevant regression
 370 coefficients. In order to make the coefficients directly comparable, independently of the order of magnitude of the
 371 variables, the independent variables were range-scaled between 0 and 1: each value was subtracted of the minimum
 372 value, and this difference was divided by the difference between the maximum and the minimum value of the
 373 considered variable.
 374 As for the significance of the variables, it was evaluated by comparing the absolute numerical value of each regression
 375 coefficient with the null value, by a t -test. If the corresponding p -value is low this means that the coefficient is very far
 376 from zero, hence it is significant and the relevant variable significantly influences the response; otherwise, the
 377 coefficient is not significantly different from zero, meaning that the corresponding variable does not influence the
 378 response. The significance of a variable increases with decreasing the p -value of the corresponding regression
 379 coefficient, in the t -test comparing it with the null value.

380

381 2.4.2 PCA

382 Principal Components Analysis (PCA) is an explorative chemometric tool, allowing to plot the objects (rows of the
 383 dataset) as points in a strongly informative plot, called scores plot, whose axes are called Principal Components (PCs).

384 To create a scores plot, the m -dimensional space formed by the original variables is rotated towards a new
385 mathematical space, where the first axis (PC1) is the one containing the maximum information (explained variance,
386 EV); the remaining $m-1$ axes are orthogonal to each other and sorted in order of decreasing EV. Plotting the scores
387 relevant to a PC (for instance PC1) vs. the scores relevant to another PC (for instance PC2), one can project the objects
388 onto a highly informative plot and view the object as points in this plot. Once calculated the PCs, one can choose to
389 further modelling data using only the first M scores which give an adequate cumulative EV. For instance, distances
390 between objects will be calculated using the first M scores. Distances allow exploring eventual differences between
391 the objects. Two distances are particularly useful: the distance between a point on the scores plot and the origin of
392 the plot is called Hotelling distance (T^2) and is characterized by a threshold depending on the chosen significance; the
393 distance between an object and the scores plot, calculated as perpendicular distance out of the plane, is indicated as
394 Q ; also, for Q a threshold can be calculated depending on significance. The plot reporting T^2 vs. Q is called influence
395 plot; it allows to find out objects that far exceed the thresholds, and also the variables responsible for this diversity.

396

397 **2.5 Time periods considered**

398 In Italy, the so-called first wave of the pandemic involved many people and very severe health effects occurred leading
399 the national authorities to establish a lockdown strategy from the 8 March 2020 to the 18 May 2020 (DPCM 8 March
400 2020; DPCM 9 March 2020); the sequence of restrictions during the first wave impacted on personal mobility which, in
401 turn, was found to account for the spreading of the pandemic in the first wave (Gatto et al. 2020; Carteni et al., 2020).
402 After the 18 May the number of infections continued to slow down, all public shops, bars, restaurants, sporting
403 centres, theatres, and cinemas were open, people were free to move within regional territories (except various needs)
404 and the use of personal surgery mask was mandatory only in closed places (DPCM 17 May 2020). This is the beginning
405 of a period with “quite” pandemic diffusion (Fig.2) not mitigated by severe restrictions, so it was chosen as a reference
406 time to test possible effects of the atmospheric parameters under relatively large freedom of personal mobility,
407 possibly also dealing with psychological feeling of relaxation and trust. We have indicated this time period in a concise
408 way adopting the informal label “free/summer period”. This term is used also thereafter. The free/summer period
409 ended on the 6 November, when new drastic restrictions were established after a sudden increase of cases observed
410 during October (night curfew, halved occupancy of public transport, closure of high schools, partial or total closure of
411 shops depending on the severity of the pandemic diffusion) (DPCM 3 November 2020). The fast increase of infections
412 during October in the whole nation was the beginning of the so-called “second wave” during which a weekly

adjustment of the restrictions was taken for the different regions according to the number of infections and availability of hospital care. Several limitations to the normal human activities were introduced or removed in the different Italian Regions; moreover, during the Christmas period (and the pre-Christmas shopping time) the changes of rules were even more frequent. The second wave developed in a diachronous way through Northern Italy, more severe and early in western regions (Fig.2). In order to test possible effects of the atmospheric parameters under a strong limitation of personal mobility and possibly psychological feeling of stress, a reference time period was chosen from the 14 November up to the end of the year, beginning a few days after the activation of the new rules, to make our system stable for our analysis. We have indicated this time period in a concise way adopting the informal label “confined/autumn period”. This term is also used thereafter.

3. Results

3.1 Delay between environmental stress and hospitalization

The scanning of progressive lag time for the free/summer period shows that the best fit between the model and the observed data (RCS) occurs for a delay between 14 and 16 days for most areas. The standard deviation against the lag time (days) reported in Fig.3 shows that the errors decrease approaching the lag time corresponding to the best fit and then increase again. The trend is regular and it is very easy to identify the lag time for the lowest standard deviation. For Val d’Aosta, the lag time is represented by a flat interval of minimum values between 14 and 18 days (17 days represent the lower standard deviation because of a very little difference in comparison with the other days). Only for Lombardia, there is a continuous decreasing trend, never seen in the other areas; in this case, a relative minimum at 18 days was identified and chosen as lag time.

For the confined/autumn period the lag time is a bit higher (18-21 days) but the shape shown by standard deviation values is more irregular respect to the previous period (Fig.3). In particular, for three areas (Val d’Aosta, Veneto and Emilia Romagna) there is an early minimum at 10-12 days, not reliable as defined by only one isolated point (Veneto) or too much early (Aguilar et al., 2020; Argenziano et al., 2020); in Val d’Aosta, Veneto and Emilia Romagna the shape of the standard deviation points is rather flat, even if a minimum value can be identified.

3.2 The multivariate model

The results of the multivariate analysis developed after the identification of the lag time are reported in Fig.4 in terms of significance F of the model (ANOVA p-value of the model, briefly here indicated as p_F), the significance of the

442 statistical coefficients (p-value of t-test) and coefficient values. The coefficients represent also the load of the factors
 443 as they were rescaled from 0 to 1 (Brereton, 2007). Figures of merit are also reported in Table 1. Detailed regression
 444 coefficients are reported in Table S1, together with relevant standard deviations (Std.e.) and p-values of t-test for the
 445 comparison with the null value.

446 For the free/summer period the significance of the model is always very high, corresponding to very low p-values of F-
 447 test on the model ($10^{-26} - 2 \cdot 10^{-65}$). The R values are always very high: there is strong correlation between the response
 448 and the factors; the R_{cv} show very high values for all regions: the capability of the models to predict is surprisingly
 449 high. Several atmospheric parameters and also many interactions are significant or very significant. An additional
 450 feature deals with the sign of the coefficients of T, S and P: these parameters have a known effect on the viability or
 451 infectivity of the SARS-CoV-2 coronavirus, according to controlled laboratory conditions or considering the deleterious
 452 effect of particulate matter on human health (see section 1). For most of the areas the multivariate analysis gives rise
 453 to very significant coefficients of T, S and P and their signs agree with the results of the mentioned literature. The
 454 coefficients of relative humidity are always negative and for all the areas (but Lombardia) are also significant or very
 455 significant. The wind speed results at least significant in three areas, with a negative sign.

456 As for the interactions, the p-values relevant to their regression coefficients quantify their importance: for low p-
 457 values a strong synergy of the two multiplied variables is unveiled. A remarkable and novel result is that in several
 458 cases the interactions are significant or very significant; T·S is very significant in 7 areas over 8 (Lombardia is the
 459 exception) and with high load: this means that the simultaneous variation of T and S results in a strong effect on RCS;
 460 as for the sign of this effect, it is accordingly to the signs of the regression coefficients of the single variables, as long
 461 as these coefficients are significant. In fact, when a regression coefficient is not significant, it means that it is not
 462 different from zero, hence its sign has no experimental meaning. All the interactions turn out to be at least significant
 463 in one area, even if S·P, S·H, and S·W are significant only for one of the considered areas. There is no interaction which
 464 never gets significant levels.

465 Considering the confined/autumn period, the R values are always very high, indicating a strong correlation between
 466 the response and the factors; the R_{cv} show very high values, with the only exception on Emilia-Romagna in which the
 467 predictive ability is significant but not high: but in all the other regions the capability of the models to predict is again
 468 surprisingly high. The RMSE and $RMSE_{cv}$ are in all cases very low, considering that the maximum value for y is in the
 469 order of hundreds. As for the regression coefficients, the results are less homogeneous and the coefficients which are
 470 significant or very significant are fairly less frequent. A peculiar feature regards the sign of the coefficients for T, S and

471 P, which only in five cases are at least significant, but with a sign opposite with respect to the results of the
472 free/summer period. The coefficients of the three factors are never significant (W, S·P and W·P).

473

474 **3.3 PCA: Influence plots**

475 As an example, the Influence Plot relevant to Val d'Aosta in the confined/autumn period is reported (Fig.5). The
476 reported plot has been computed using the first four PC, containing 93.4% of the full EV. It is evident that the object
477 15/12 (15 December) is very far from the T^2 threshold. The variables responsible for this diversity are W and W·P. The
478 complete analogous analysis of the influence plots for the free/summer period and for the confined/autumn period is
479 reported in Table 2. For the free/summer period, three regions (Val d'Aosta, Trento, Friuli Venezia Giulia) show
480 outliers in June, all related to the interaction S·H; all regions except Veneto and Friuli Venezia Giulia show outliers in
481 October, with no particular regularity as regards responsible variables: several interactions are involved, while the
482 effect of single variables on outliers is observed for Val d'Aosta (P), Piemonte (W), Emilia-Romagna (S); all regions
483 except Val d'Aosta and Emilia-Romagna show outliers in early November, and in this case P is always involved, as a
484 single variable or in interaction with others.

485 As for the confined/autumn interval, few outliers are present between 12 and 26 December, and the main factors
486 involved are the single variables P and W, and several interactions (with W·P particularly recurring, in the regions Val
487 d'Aosta, Piemonte, Lombardia, Bolzano).

488

489 **4. Discussion**

490 **4.1 The lag time**

491 The blind search for an appropriate lag time developed in this study is consistent with other studies that take into
492 account the hospitalized cases as a measure of the pandemic spread (Lolli et al., 2020). The time period between the
493 atmospheric stress and hospitalization agrees with clinical observations (Aguilar et al., 2020; Argenziano et al., 2020)
494 According to these researchers a brief period of 3-5 days occurs between the infection and the insurgence of
495 symptoms, then during the successive 5-7 days the first stage of the clinical course is concluded with mild symptoms.
496 In the following 10-14 days a possible progressive worsening of individuals' clinical status may arise, leading to the
497 need of hospitalization (Aguilar et al., 2020). The hospital load is a significant sign of the stress suffered by the sanitary
498 system and of the socio-economic impact due to working days lost. The agreement of our results with the biological
499 criteria adopted to compute incubation-latency period validates the approach used for this study (and in other cases,

e.g. Pirouz et al., 2020; Adhikari and Yin, 2021) and can be helpful for predictive purposes of SARS-CoV-2 recurrence. A significant finding is the longer lag time observed under confined conditions (17-21 days) with respect to the free period (15-17 days), suggesting that the preventive measures are effective in diluting the load of hospitalization over a wider time span (Pana et al., 2021).

4.2 The effect of atmospheric variables emerging from Italian studies

In Italy the pandemic developed earlier in comparison with other countries (Lolli et al., 2020; Wu et al., 2020a), therefore a lot of studies have been published on this topic. These investigations have examined the effect of atmospheric parameters on the COVID-19 diffusion in the most impacted zone (especially Lombardia, and its main city: Milano), and during the most dramatic period, up to March 2020, i.e. the first month (Pivato et al., 2021; Pirouz et al., 2020; Collivignarelli et al., 2021; Haghshenas et al., 2020; Bontempi, 2020; Passerini et al., 2020; Ye et al., 2021; Sfica et al., 2020; Khurshed et al., 2021; Coker et al., 2020; Bianconi et al., 2020; Accarino et al., 2021; Perone, 2021; Filippini et al., 2021; Kotsiou et al., 2021), or up to April 2020 (Coccia, 2020; Delnevo et al., 2020; Fazzini et al., 2020; Filippini et al., 2020; Fattorini and Regoli, 2020; Zoran et al., 2020; De Angelis et al., 2021; Benedetti et al., 2020; Agnoletti et al., 2020). Only a few works have considered a wider time span, up to the end of spring (Ho et al., 2021; Pansini and Fornacca, 2021; Lolli et al., 2020; Cascetta et al. 2021). The paper by Fiasca et al. (2020) has studied the effect of air pollution until the end of November. Our analysis covers a bit different time periods and conditions because we considered what happened after the effective diffusion of the SARS-CoV-2 virus over the study area (as shown by the occurrence of cases and recoveries in all the regions), a circumstance resembling the actual conditions and possibly our near future.

4.2.1 The effect of atmospheric variables during the free/summer period

The more evident role of atmospheric variables can be seen during the free/summer period, when the significant parameters are more abundant and with similar effects in different areas (Fig.4a) with respect to the confined/autumn period (Fig.4b). The most important meteorological factors are represented by T and S, which show a protective role in 7 areas over 8 (only T in Lombardia). The protective effect of T has been widely recognized in North Italy (Benedetti et al., 2020; Lolli et al., 2020; De Angelis et al., 2021; Perone, 2021; Coker et al., 2020; Khurshed et al., 2021). However, this relationship was not significant during the first month from the starting of the Sars-CoV-2 pandemic. (Pirouz et al., 2020; Haghshenas et al., 2020). An adverse effect of the variable T during the first

month since the beginning of outbreak has been reported just in Lombardia, where a positive correlation with new cases has been observed (Passerini et al., 2020).

The effect of S on the viral spreading capability has been rarely investigated in Lombardia (Fazzini et al., 2020) and in Italy (Sfica et al. 2020), but the results are not univocal. Furthermore, an interesting new finding emerges from our analysis: the interaction between the T and S variables generates a protective effect against SARS-CoV-2 diffusion in the population. This action is highly significant in 7 areas over 8 (Fig.4a), and it has been never noticed previously. The idea that T and S can play synergic effects against respiratory viruses agrees also with the studies based on machine learning and laboratory investigations, concerning the spread of the influenza virus in Northern Europe (Ianevski et al., 2019). Sunlight may provide protection to humans against SARS-CoV-2, by means of a double action. It has been suggested that UV-B radiation may inactivate or damage the virions and may improve the immune system activity of individuals. Some reports have suggested that VD exerts protective effects, by inhibiting virus transmission, via direct inhibition of the interaction between viral spike protein and ACE-2 receptor on cell membrane surface (Shoemark et al., 2021), or by improving immune system responses. Therefore, its use has been proposed in the initial phase of SARS-CoV-2 associated pandemic, since March 2020, with preventive or therapeutic purpose in patients with COVID-19 at higher risk of developing severe forms of diseases, such as aged people or immunocompromised individuals (Fiorino et al., 2020; 2021a). Several meta-analyses have confirmed these preliminary suggestions and have reported that individuals with vitamin D deficiency are at higher risk of SARS-CoV-2 infections and of a poorer clinical outcome in comparison with subjects with normal levels of this micronutrient, (Kaya et al., 2021; Ghasemian et al., 2021; Szarpak et al., 2021; Oscanoa et al., 2021) whereas only a few studies have examined the effects of vitamin D supplementation in patients suffering from COVID-19. Although these investigations have shown interesting results, the number of enrolled individuals is small. Therefore, no definitive conclusions may be drawn and further trials are needed to clarify this topic (Entrenas Castillo et al., 2020; Elamir et al., 2021).

The effect of H on the pandemic diffusion has been debated and it still results unclear at a global scale (see 1.1.1) also in North Italy, where an increase of the pandemic effects has been associated with higher humidity (Pirouz et al., 2020; Haghshenas et al., 2020; Perone, 2021; De Angelis et al., 2021, for absolute humidity), although opposite conclusions have been also reported (Passerini et al., 2020; Khursheed et al., 2021; Zoran et al., 2020; Lolli et al. 2020; Zhu et al., 2020, for absolute humidity). Fazzini et al. (2020) has found no significant effects. In the free/summer period the protective effect of H has been observed in the study area (Fig.4a). Lombardia also has shown the same trend but without reaching a statistical significance. A pivotal role of H, poorly noticed before, arises also by the

occurrence of significant interaction with S (Val d'Aosta), P (Piemonte and Bolzano), T (Trento and Bolzano) and W (Trento and Bolzano).

Among the parameters considered, only W is rarely very significant, with some exceptions. In these cases, a lower number of hospital admissions is systematically observed during stronger windy days. A possible weakness of W, as a significant factor, agrees with other studies in the considered area (Haghshenas et al., 2020; Passerini et al., 2020; Fazzini et al., 2020; Lolli et al., 2020), only in Veneto a protective effect has been reported but it has been described only during the first month of pandemic (Pirouz et al., 2020). It could be mentioned that the wind speed and direction is severely conditioned by the position and extension of buildings in urban centres, so, the wind experienced by urbanized citizens could differs with respect to the meteorological data.

A more difficult task is to evaluate the role of P, because air pollution is highly significant only in the mountain areas (Val d'Aosta, Trento and Bolzano; Fig. 4a), with a negative connotation for the health, according to the well-known deleterious effect of particulate matter on the human health. However, in Lombardia and Veneto, the most polluted regions among those considered (for instance Stafoggia et al., 2020), only the tendency of P to increase the RCS is confirmed, but without significant p-values. The positive relationship between particulate matter pollution measured each day and the spreading of COVID-19 was already observed in the Trento area (Lolli et al., 2020), whereas in Lombardia a more delimited area around the metropolis of Milano was studied, confirming the same effects up to April (Zoran et al., 2020) and June 2020 (Lolli et al., 2020). Other studies about the role of particulate matter on the COVID-19 were performed for the areas studied also in the present work and following similar approach (comparison between day by day parameters of particulate matter pollution during the pandemic and health effects); despite the previous studies consider an earlier time period, their conclusions are in agreement with our results: the daily air pollution does not seems a crucial factor in modulating the pandemic diffusion in North Italy (Bontempi et al., 2020; Collivignarelli et al., 2021). A similar daily-based study was carried out in Emilia-Romagna, considering several air pollutants (PM₁₀, PM_{2.5} and NO₂: Mirri et al., 2020) or following a Granger causality statistical hypothesis (Delnevo et al., 2020), that was designed to handle pairs of variables and could suffer when additional variables take part in the relation. Under such Granger causality perspective, a positive correlation between particulate matter and COVID-19 diffusion is observed up to the first 8 weeks of local pandemic, but this result still refers to an earlier time period respect to our study. Additionally, the results by Mirri et al. (2020) are very interesting and show that within the same region (Emilia-Romagna) each of the 9 provinces should be analyzed separately to account for the COVID-19 occurrence; unfortunately, such operation is not possible as the number of individuals hospitalized in general medical

wards is provided in aggregate form. The need for detailed local research, focusing on epidemiologic-environmental relationships, emerges also from the spreading of COVID-19 in Catalonia (Tobías et al., 2021), and also from studies on the effect of particulate matter on other pathologies (for instance Scartezzini et al., 2021).

The evaluation of several polluting factors (O₃, NO₂, SO₂ in addition to PM₁₀ and PM_{2.5}) by Ho et al. (2021) has led to finding that only the chronic pollution by particulate matter is significant for COVID-19 effects in Lombardia and Veneto, whereas on a daily basis the PM₁₀ and PM_{2.5}, are not, up to May 2020. A different conclusion was proposed by Ye et al. (2021) in the same time period (up to May 2020). The researchers have observed a significant impact of PM on all-cause mortality during the pandemic period. The latter study differs from our approach, because these authors have considered a very short lag time (0-3 days), and all the Italian territory, which includes areas with different socio-economic status. This aspect represents a known confounding effect in epidemiological studies (Rosano et al., 2020). The association between COVID-19 incidence rates and PM_{2.5} pollution was observed during the COVID-19 period in Italy over a more extended period (up to 3 November 2020, Fiasca et al., 2020) and during the first wave (1 January - 31 March 2020, Accarino et al., 2021) but these studies have compared different individual provinces, whereas our approach is to check for a possible day by day association between the RCS and atmospheric parameters within each single administrative area.

Despite the daily variations of PM does not seem to represent an essential factor in highly populated plain areas from our data, a different role emerges when the effect of long-term pollution of particulate matter (years-months) is taken into account, according to the evidence available in the literature. Several studies have considered this effect in Italy and have reported higher pandemic diffusion in more historically polluted areas (Bianconi et al., 2020; Coker et al., 2020; Fattorini and Regoli, 2020; Cascetta et al., 2021; De Angelis et al., 2021; Fiasca et al., 2021; Ho et al., 2021; Kotsiou et al., 2021; Pansini and Fornacca, 2021; Perone, 2021; Ye et al., 2021). The wide plain area of the Northern Italy (Fig.1) is one of the most impacted areas for pollution by PM all over Europe (EEA, 2020). The comparison of literature data with our results shows a twofold conclusion: 1) the mountain areas studied (Val d'Aosta, Trento and Bolzano) are poorly affected by long-term PM 2.5 pollution (Stafoggia et al., 2020 and Table S2), but the day by day variation of P shows a highly significant correlation with RCS (Fig.4a); 2) in the other areas, which are severely affected by long-term PM 2.5 pollution, our data detect no significant correlation with P variations. We have no data explaining such an apparent paradox, but possible speculation is that exceeding a threshold limit, the day-by-day variation of P is not effective in changing the chronic exposure to a specific pollutant. In agreement with our findings, a recent meta-

analysis has shown that an association exists between COVID-19 mortality and long-term exposure to PM2.5 but not to short-term one (Zang et al., 2022).

A final consideration on the free/summer period refers to the number of interactions that have turned out to be significant in influencing human health (Fig.4a). Some couples of parameters (for instance temperature and particulate matter, Stafoggia et al., 2014) had been already recognized as important factors involved in this action. However, our paper reinforces this preliminary conclusion: a large spectrum of atmospheric parameters may generate cooperative interactions and produce important effects on human health.

A possible scenario showing the relationships among environmental factors and the host's defense mechanisms on the fitness and infectious capability of SARS-CoV-2 is sketched in Fig.6.

4.2.2 The effect of atmospheric variables during the confined/autumn period

During the confined/autumn period the significant parameters have resulted to be in lower number and with variable role (sign of coefficients); also, the similarities among different areas, observed in the free/summer period, are no more detectable. A possible explanation relies on the establishment of new social restrictions after the 6 November 2020. Moreover, the restrictions adopted in the different areas were not synchronous and identical (DPCM 3 November 2020), so that the effect of atmospheric factors in different areas could be different. The high efficacy of public health interventions in Italy (social distances, restrictions in public and private places, individual protective devices, etc.) had already been observed in comparison with other countries during this time period (the so-called second wave; Bontempi, 2021). A modification of the relationships between atmospheric parameters and the COVID-19 diffusion had been already observed earlier in Italy and it was due to the lockdown during the spring season (Benedetti et al., 2020; Ho et al., 2021). Also, on a global scale the public health interventions are considered to induce a major impact on the prevention of COVID-19 diffusion in comparison with seasonal factors (Juni et al., 2020; Paraskevis et al., 2021).

During the confined/autumn period some significant atmospheric parameters have acted in a surprising way, for instance T has increased the RCS in Veneto, Friuli Venezia Giulia and Emilia-Romagna, P in Bolzano has been associated with a decrease of RCS, an opposite sign has characterized H in Lombardia and Bolzano. Significant interactions occurred also in this period, the more recurrent have been T-S (Val d'Aosta, Veneto, Friuli Venezia Giulia and Emilia-Romagna) and T-H (Piemonte, Veneto, Friuli Venezia Giulia and Emilia-Romagna). The atmospheric parameters under these climatic and sociality conditions have possibly acted both directly on biological targets

644 (human immune system and the virus) and also on social behaviors, increasing or decreasing the interactions between
645 individuals according to meteorological conditions. An opposite effect was already stressed, suggesting that warm
646 days during the cold season stimulate outdoor people mobility/sociality in winter (Byass, 2020; Sfica et al. 2020).

647

648 **5. Conclusions**

649 This work accomplishes several meteorological parameters (temperature, solar radiation, relative humidity, wind
650 speed) and a well-known pollution index (PM 2.5), which is especially dangerous to human health. The multivariate
651 statistical models here developed are characterized by a very high significance, enabling a detailed evaluation of the
652 effects of the studied environmental factors on the pandemic. All the atmospheric parameters in turn play a
653 significant role in determining the hospital admission for COVID-19 during a time period subsequent to the first wave
654 of the pandemic, along about 6 months. This effect is appreciable following the daily incidence of hospitalization
655 within all the 8 territorial areas considered. The admission of people in general medical wards is not only an effect of
656 the SARS-CoV-2 spreading but also represents a social and economic load for territories. Another finding is that some
657 of the environmental parameters considered exert major rule respect to others. In particular, T is highly significant in
658 all the 8 areas, confirming the results of other studies, but our new findings stress the pivotal role of S and H, both of
659 which have an appreciable effect in 7 areas over the 8 considered; only for Lombardia, S and P are not significant,
660 which point out a particular effect of the relationship between pandemic and environment in such region.

661 The obtained results also show that the role of P deserves special attention, because in the areas with more severe
662 chronic pollution by PM the day-by-day variation of P does not load on the hospital admissions, whereas in mountain
663 territories (which are fairly less impacted by PM pollution) P is highly significant in increasing the hospitalization. The
664 reason for such different effects is beyond the aim of the present work, but considering the deleterious effect that PM
665 has on human health in general, our findings encourage more studies to be done.

666 The chemometric approach adopted allows to highlight, on a solid statistical basis, not only the role of single
667 atmospheric factors, but also of their interactions. This new approach is particularly interesting as several interactions
668 are significant or very significant in all the areas, in particular T-S plays an important role everywhere, with the
669 exception of Lombardia which is confirmed as a peculiar area also under this point of view.

670 During the beginning of the local second wave, when social restrictions occurred, the atmospheric parameters that
671 significantly influence the multivariate models are much less numerous, suggesting that people's movements and
672 sociality play a substantial effect.

673 The present work shows that several environmental parameters and their interactions should be considered in
674 fighting the pandemic. The present work shows that several environmental parameters and their interactions should
675 be considered in fighting the pandemic. Common environmental factors considered in this study can act on the
676 viability of the virus and on the efficiency of the host's immune system, as sketched in Fig.6. Despite the scheme
677 cannot be considered exhaustive lacking other considerations (for instance about mobility and sociality), it emphasizes
678 direct and cooperative effects that emerge from our study as significant in conditioning the pandemic evolution.
679 Besides the comparison of different territories (which inevitably bring their own social and environmental features),
680 also the day-by-day variations of atmospheric parameters inside a defined area can lead to reliable models of
681 pandemic diffusion, and this is especially important under the threat of increasing intensity and frequency of extreme
682 novel epidemics (Marani et al., 2021).

683

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691

692 **Appendix A. Supplementary data**

693 Supplementary data to this article can be found online.

694

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Figure captions

Fig. 1. Location of the areas under study (Regions and Autonomous Provinces: bold line); the Provinces which compose some of the areas are marked by thinner border; urban centres in black.

Fig. 2. Number of hospitalized people in general medical wards on 100000 residents (RCS). The dates of the main restriction rules are reported.

Fig. 3. Mean quadratic distance between RCS and the model obtained by multiple linear regression of atmospheric parameters shifted by 10 to 24 days.

Fig. 4. Value of the coefficients for the atmospheric parameters and p-values for the interactions obtained by MLR, computed for the lag time corresponding to the best fit between RCS and the model; the ANOVA p-value of the model is reported (p_f). The parameters with very significant p-values (< 0.01) are marked by dense pattern and orange background; a lighter pattern and yellow background is used for significant p-values (< 0.05); d= days corresponding to the lag time considered; a): free/summer period (18 May - 6 November 2020); b) confined/autumn period (4 November - 31 December 2020).

Fig. 5. Influence plot for Val d'Aosta in the confined/autumn period. Number of PCs: 4. Explained variance: 93.4%.

Fig. 6. The figure summarizes the current knowledge on the possible role of atmospheric conditions (High and Low Temperature, High and Low Relative Humidity and Solar Radiation) and of air pollutants (Particulate Matter) as well as of host's defense mechanisms on the fitness and infectious capability of SARS-CoV-2. Our analysis refers to the period, ranging from 18 May to 6 November 2020, in several regions of North Italy. Each of the above-mentioned factors may exert an its own individual activity or it may establish reciprocal interactions with the other climate-, environmental- parameters and with host's defense functions and produce a wide spectrum of effects. Experimental evidence suggests that:

A) High temperature, as a single factor or together with Solar Radiation, may reduce viability and survival of SARS-CoV-2 through a direct anti-viral effect probably by: a) decreasing the stability of virions, b) preserving the normal function of ciliate cells, preventing their damage by airborne pathogens and particulate matter, c) affecting desiccation or hydration of viral droplets, modulating the size of droplets in cooperation with Relative Humidity (see also D and E);

B) Solar Radiation, alone or in cooperation with environmental High Temperature, displays an antiviral function. Solar UV-B rays may impair the stability of viral capsids by: a) directly reducing the stability of SARS-CoV-2 virions and decreasing their fitness and survival b) indirectly promoting an increase in vitamin D synthesis. This fat-soluble micronutrient regulates the normal activity of different components and elements, belonging to immune system. An adequate antiviral response by host requires a cooperative interplay among these elements, such as cells (lymphocytes/macrophages) and mediators (chemokines, interleukins and oxygen species). Vitamin D3 may contribute to restore a proper function of both innate and adaptive arms of immune system. In particular, SARS-CoV-2 and particulate matter may impair the functionality of both lymphocytes and macrophages, via different mechanisms.

1186 Vitamin D3 may counteract the harmful effects caused by virus and by air pollutants and it may promote the
1187 reactivation of an adequate antiviral response by lymphocytes and macrophages in the host;

1188 C) Low Temperature as a single factor may promote SARS-CoV-2 infectious capability and its survival by: a) impairing
1189 host's defences in respiratory tract, via the damage of barrier system (the mucus layer, the surface liquid layer and the
1190 cilia on the surface of the bronchus epithelia) as, in normal conditions, these factors are able to counteract virus entry,
1191 or via the alteration of innate and adaptive immune response (the network of interferons, macrophages, lymphocytes
1192 and interleukins/cytokines) as these elements may block the virus which has by-passed the host's barrier system (b)
1193 affecting the physical characteristics of droplets, which carry the virus. In particular, Low Temperature alone or in
1194 cooperation with Low or High Relative Humidity may modulate the size of droplets, carrying SARS-CoV-2 and
1195 therefore it may influence the capability of this pathogen to infect the host (see also D and E);

1196 D) Low and E) High Relative Humidity as single factors may promote the desiccation or hydration of droplets, carrying
1197 SARS-CoV-2, and therefore they induce a reduction or an increase in their sizes. These events may influence the
1198 infectious capability of the virus, but the data available in literature are not univocal. In particular, data emerging from
1199 our analysis indicate that High Relative Humidity is associated with low rate of hospital admission. The role of Relative
1200 Humidity is debated and represents a proper example of how the mutual interplay among atmospheric,
1201 environmental and host's factors impacts on the virus spreading and on human health. In particular, it is possible that
1202 the size of droplets may exert a critical role in influencing the capability of SARS-CoV-2 to spread in the environment
1203 and to infect the host. It is probable that Low Humidity itself decreases viral viability and alone or with the
1204 concomitant presence of elevated temperature induces the formation of droplets containing viral particles with a
1205 reduced fitness and having suboptimal sizes for the spreading in the environment and for the entry in host's
1206 respiratory tract. On the other hand, High Relative Humidity may increase SARS-CoV-2 fitness and infectious
1207 capability, but, even in presence of low temperature, it may promote the generation of bigger droplets, but having
1208 sizes not adequate for a proper diffusion and infectivity of the virus. All these considerations may contribute to explain
1209 the not univocal data detectable in literature, concerning this topic. It is possible that the final effects depend on the
1210 overall balance among all these interactions.

1211 F) Particulate matter may affect SARS-CoV-2 infectivity and spreading, by: a) impairing several host's functions. The
1212 most important alterations induced by air pollution include a decrease in macrophage and lymphocyte activity, a
1213 reduction of antioxidant cell systems as well as an increase of protease generation. Furthermore, particulate matter
1214 may increase RAAS activation. A further possible effect of particulate matter is to act as carrier of droplets.

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RAAS: Renin-Angiotensin-Aldosterone-System; ROS: Reactive Oxygen Species generation; SARS-CoV-2: Severe-Acute-Respiratory-Syndrome associated with Coronavirus 2.

Green arrows indicate protective antiviral actions, mediated by environmental- and atmospheric-factors as well as elicited by host's defensive mechanisms.

Red and black arrows indicate harmful viral activities, induced by environmental- and atmospheric-factors as well as elicited by host's responses.

Green lines with flat termination indicate inhibitory actions of environmental- and atmospheric-factors as well as of host's responses against SARS-CoV-2 with protective antiviral effects.

Red lines with flat termination indicate harmful actions of SARS-CoV-2, inhibiting host's protective antiviral functions.

Fig. S1. Comparison between the mean quadratic distances obtained using only five atmospheric parameters (T, S, P, H, and W) respect to the ones obtained using also their interactions (T S, T P, T H, T W, S P, S H, S W, P H, P W, and H W) (see text for explanations).

Table captions

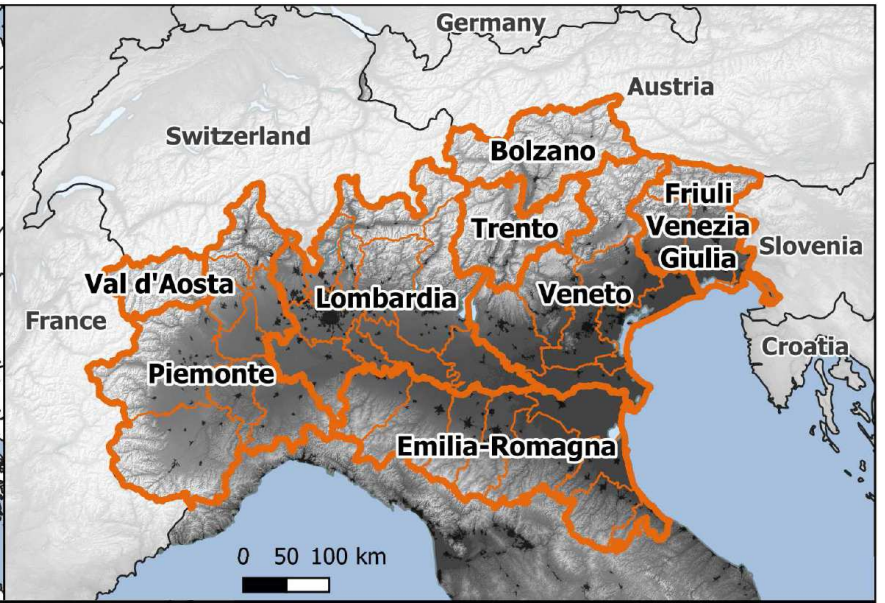
Table 1 - Figures of merit for all the MLR models created. Cross-validation: full.

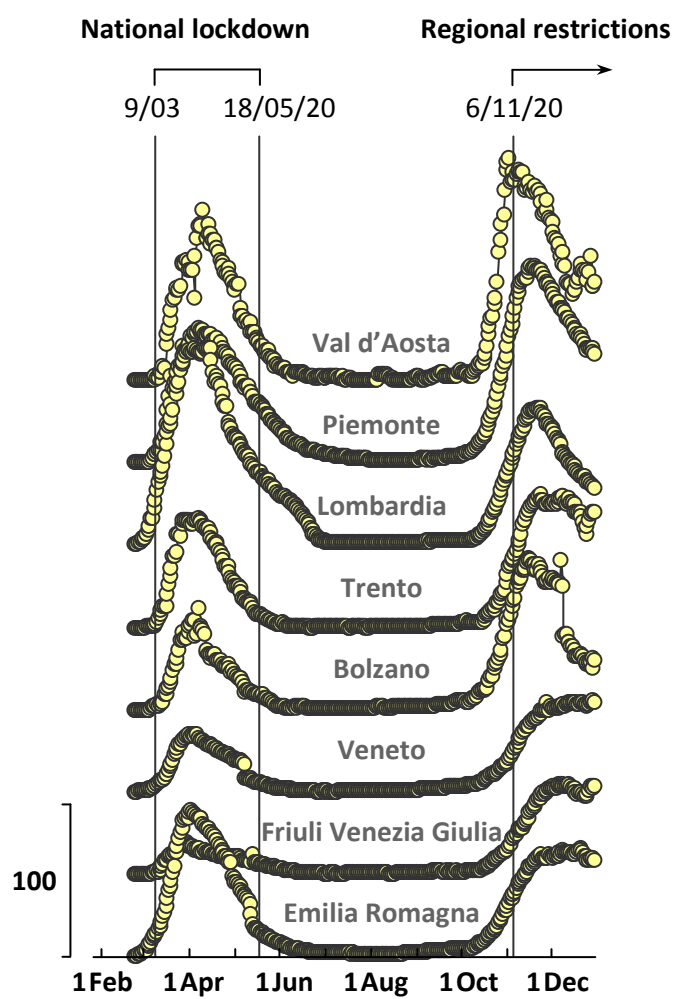
Table 2 - Analysis of the influence plot (Principal Components: 4, significance for threshold: 0.05).

Table S1a - 18 May - 6 November 2020: "free/summer period": detailed regression coefficients and relevant standard deviations (Std.e.) and p-values of t-test for the comparison with the null value.

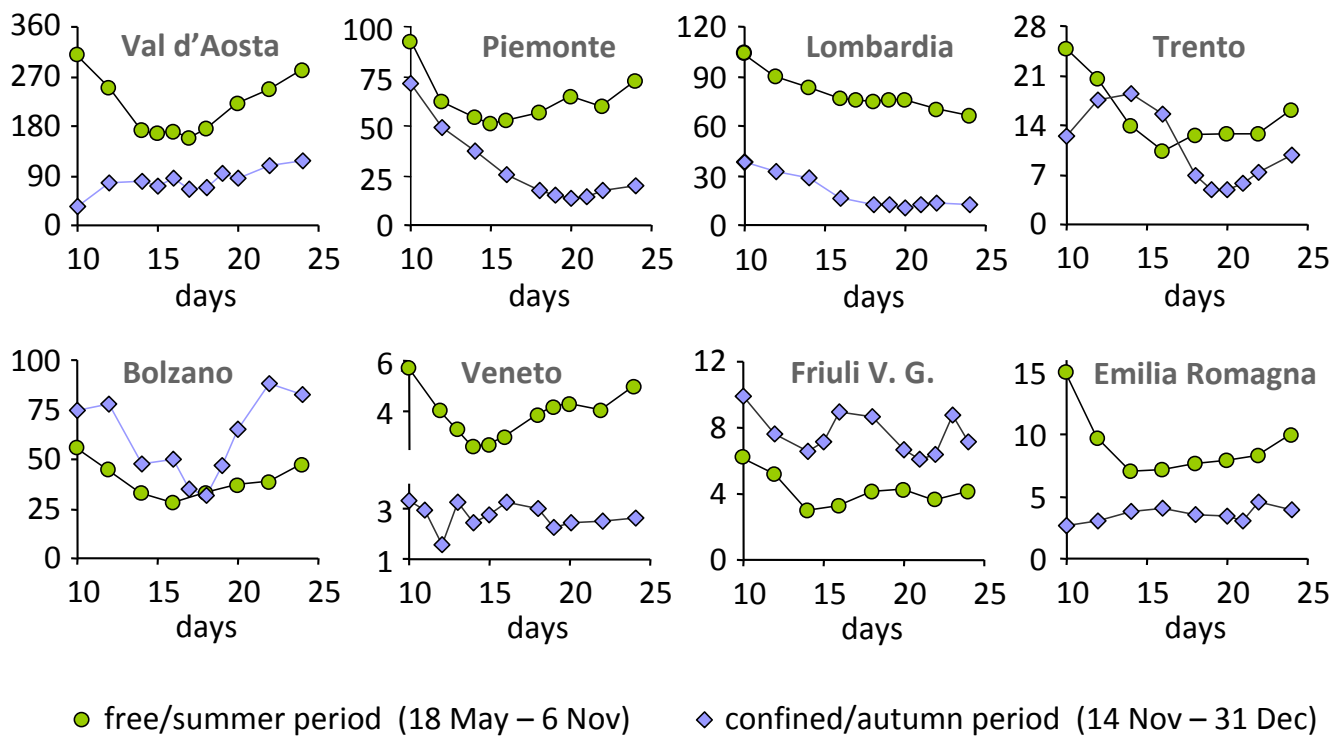
Table S1b - 14 November - 31 December 2020: "confined/autumn period": detailed regression coefficients and relevant standard deviations (Std.e.) and p-values of t-test for the comparison with the null value.

Table S2 - Annual median values of PM 2.5 ($\mu\text{g}/\text{m}^3$) from 2009 to 2018 (van Donkelaar et al., 2019; Hammer et al., 2020). The target guideline values by WHO are reported too (WHO, 2021).

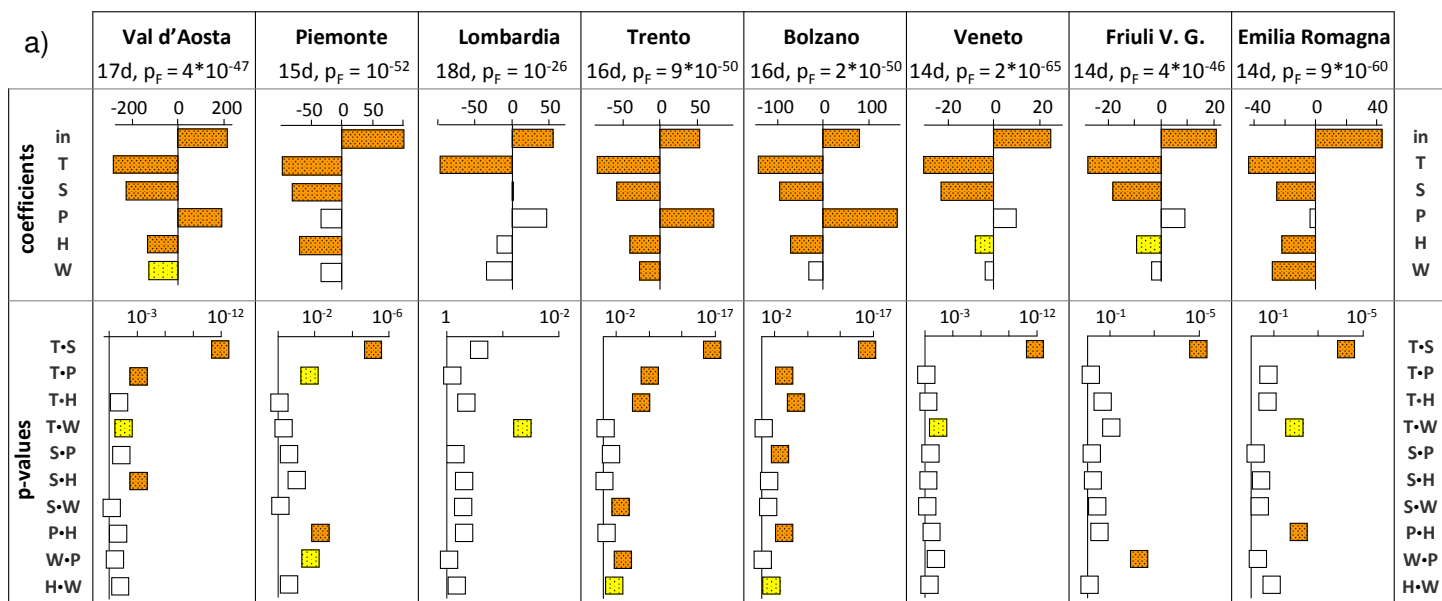




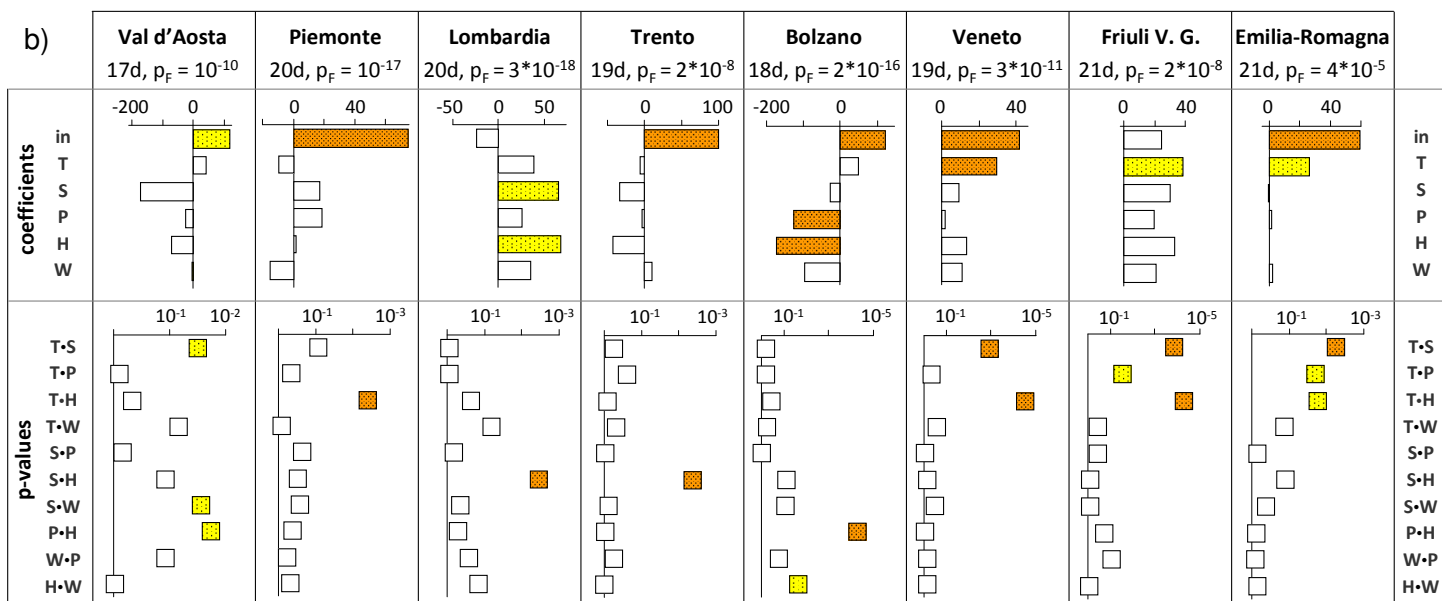
Mean quadratic distance

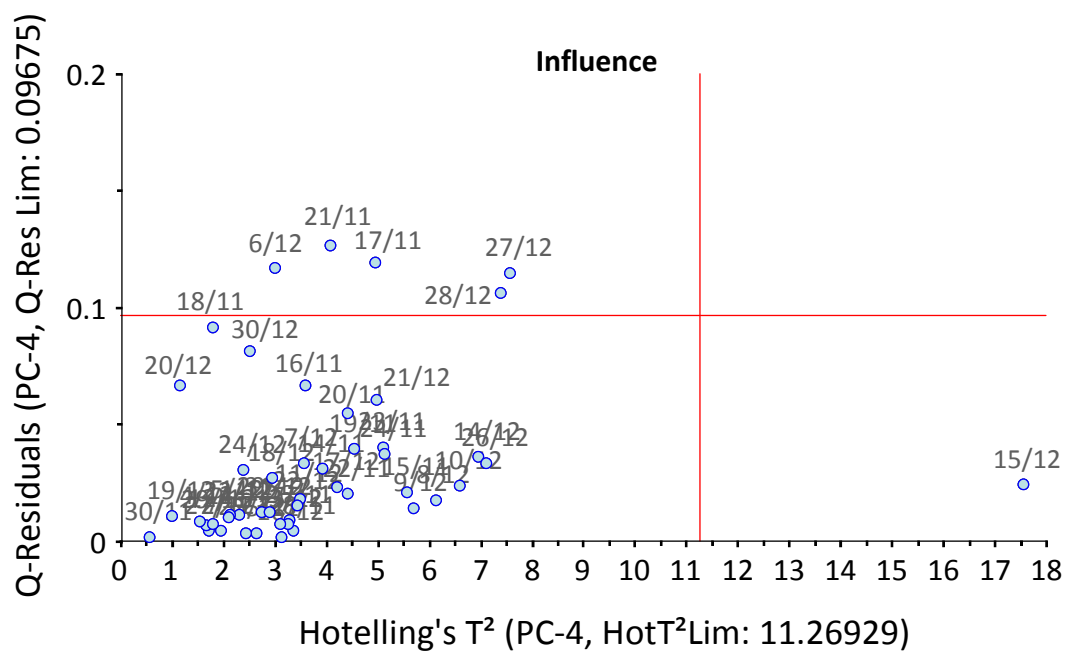


Free/summer period (18 May – 6 November 2020)



Confined/autumn period (14 November – 31 December)





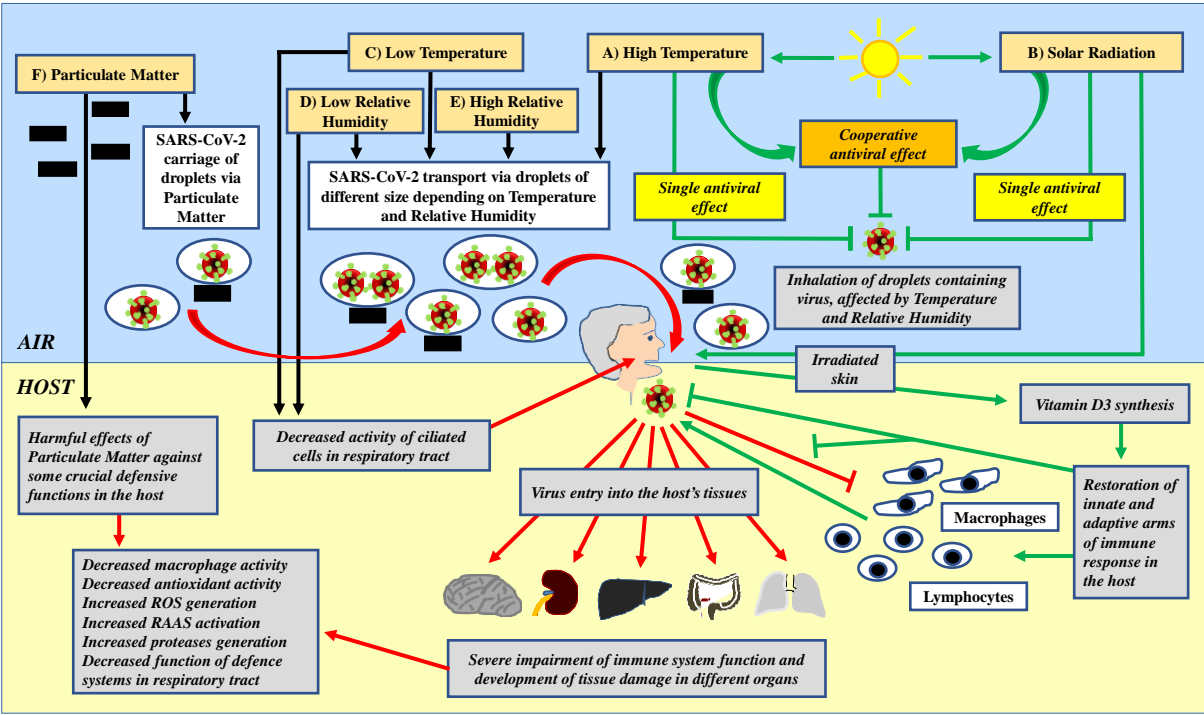


Table 1**Figures of merit for all the MLR models created. Cross-validation: full**

	free/summer period				confined/autumn period			
	R	R _{CV}	RMSE	RMSE _{CV}	R	R _{CV}	RMSE	RMSE _{CV}
Val d'Aosta	0.895	0.861	13.1	14.3	0.937	0.803	9.87	13.9
Piemonte	0.911	0.887	7.48	8.02	0.979	0.921	4.45	2.64
Lombardia	0.794	0.729	9.05	9.74	0.981	0.955	4.05	1.80
Trento	0.903	0.868	3.35	3.70	0.911	0.746	2.71	3.61
Bolzano	0.905	0.870	5.53	6.13	0.981	0.955	4.07	5.07
Veneto	0.940	0.917	1.66	1.86	0.944	0.875	1.87	2.26
Friuli Venezia Giulia	0.893	0.843	1.83	2.10	0.910	0.767	3.02	3.84
Emilia-Romagna	0.929	0.904	2.78	3.07	0.847	0.427	2.13	2.97

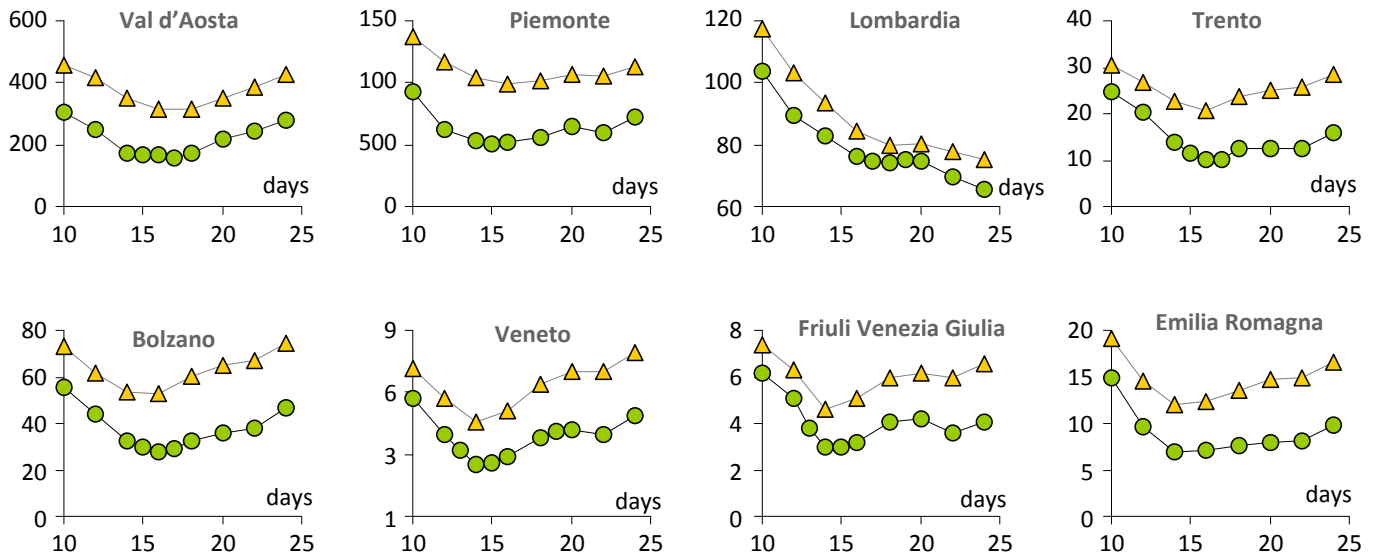
Table 2

Analysis of the influence plot (Principal Components: 4, significance for threshold: 0.05)

	free/summer period			confined/autumn period		
	EV	objects far outside threshold	responsible variables	EV	objects far outside threshold	responsible variables
Val d'Aosta	90.9%	4/6; 5, 12/10	S·H; P, S·P, T·P	93.4%	15/12	W, W·P
Piemonte	91.6%	10, 12/10; 4/11	W; W·P	91.8%	18/12	W, W·P
Lombardia	92.5%	23/9; 13/10; 6/11	S·P, T·P; W·S; S·P, T·P, P·H	92.6%	18/12	P, W, W·P
Trento	94.0%	27/6; 31/10; 5/11	S·H; S·T, W·S; P, P·U	93.2%	24/12, 25/12	S·P, T·H
Bolzano	93.9%	18/10; 5/11	S·H, P·H; P, P·H	92.6%	18/12, 26/12	P, W, W·P
Veneto	93.1%	22/8; 4/11	S·H; P, P·H	94.0%	25/12	W, W·H
Friuli Venezia Giulia	91.0%	24/6; 4/11	S·H; P, P·H	92.9%	20/12	W
Emilia-Romagna	92.9%	10/10	S, W·U	92.9%	12/12	W·S

supplementary

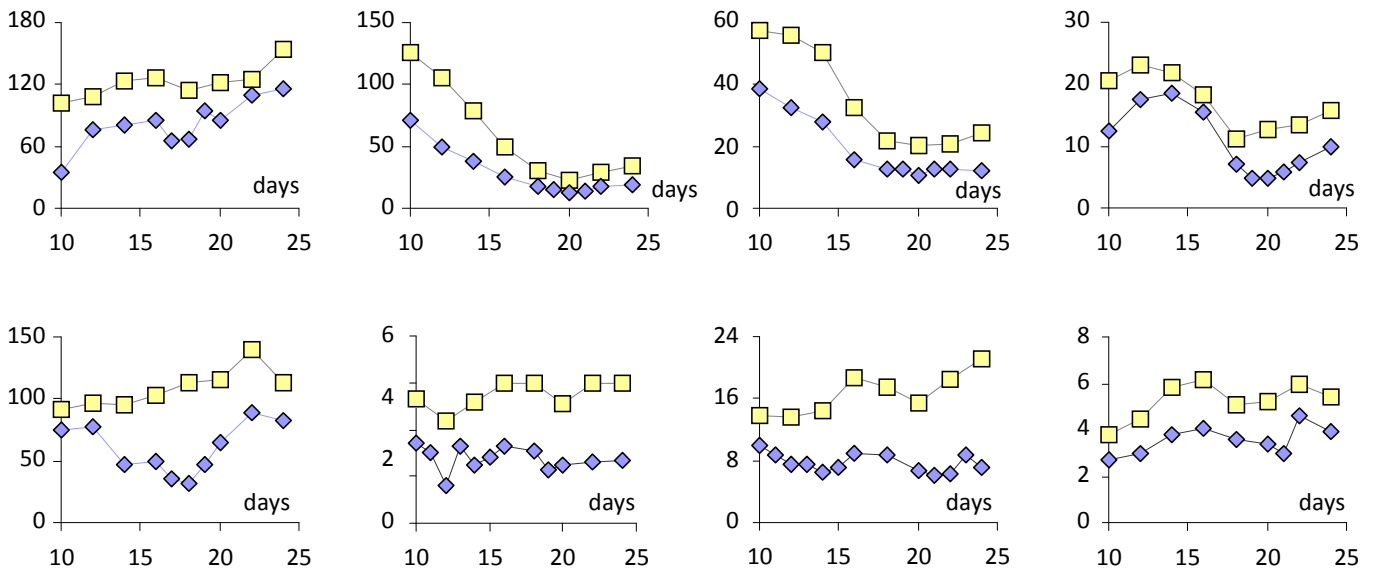
Mean quadratic distance (RCS: observed vs. calculated, 18 May - 6 November 2020: "free/summer period")



▲ 5 atmospheric parameters

● 5 atmospheric parameters and their interactions

Mean quadratic distance (RCS: observed vs. calculated, 14 november – 31 december": "confined/autumn period")



■ 5 atmospheric parameters

◆ 5 atmospheric parameters and their interactions

Supp. Table 1a

18 May - 6 November 2020: "free/summer period": detailed regression coefficients and relevant standard deviations (Std.e.) and p-values of t-test for the comparison with the null value

	Intercept	T	S	P	U	W	S-T	T-P	T-U	W-T	S-P	S-U	W-S	P-U	W-P	W-U	p _F	Lag days
Val d'Aosta																		
Coeff.	213.2	-284.7	-229.1	190.9	-132.5	-128.5	312.7	-118.9	68.6	83.3	-91.0	96.1	29.0	-85.2	52.8	103.1	4E-47	17
Std.e.	33.9	43.4	33.3	60.6	32.1	53.8	40.5	35.0	39.4	38.4	47.7	27.9	56.4	55.5	45.8	55.4		
p-values	3E-09	7E-10	1E-10	2E-03	6E-05	2E-02	1E-12	9E-04	8E-02	3E-02	6E-02	7E-04	6E-01	1E-01	3E-01	6E-02		
Piemonte																		
Coeff.	101.4	-98.0	-81.3	-35.1	-69.1	-34.5	103.8	-57.8	-3.1	17.4	38.1	28.7	-12.9	100.9	65.5	36.8	1E-52	15
Std.e.	20.8	27.4	23.7	32.0	22.8	27.0	22.4	24.4	27.8	28.7	33.6	17.2	37.9	35.7	27.6	33.8		
p-values	3E-06	5E-04	8E-04	3E-01	3E-03	2E-01	8E-06	2E-02	9E-01	5E-01	3E-01	1E-01	7E-01	5E-03	2E-02	3E-01		
Lombardia																		
Coeff.	56.2	-97.2	2.7	47.8	-19.4	-33.8	27.9	-8.2	24.3	73.4	-20.6	-11.3	-28.5	-33.4	-4.0	16.0	1E-26	18
Std.e.	19.5	29.6	25.6	43.3	21.9	30.3	25.0	33.1	31.7	36.4	54.9	16.5	43.3	49.2	40.6	36.3		
p-values	5E-03	1E-03	9E-01	3E-01	4E-01	3E-01	3E-01	8E-01	4E-01	5E-02	7E-01	5E-01	5E-01	5E-01	9E-01	7E-01		
Trento																		
Coeff.	53.0	-84.9	-59.6	73.0	-41.7	-28.3	93.4	-57.6	60.3	7.4	-27.3	3.9	32.3	-17.8	-26.5	22.5	9E-50	16
Std.e.	7.1	10.9	7.8	15.3	9.1	9.1	9.8	10.4	12.2	9.2	15.8	6.9	10.5	16.9	8.0	10.0		
p-values	7E-12	7E-13	3E-12	4E-06	9E-06	2E-03	4E-17	1E-07	2E-06	4E-01	9E-02	6E-01	2E-03	3E-01	1E-03	3E-02		
Bolzano																		
Coeff.	79.0	-141.3	-93.8	161.3	-71.5	-30.8	165.5	-65.2	106.1	-12.4	-108.3	19.3	37.6	-109.2	-5.7	42.7	2E-50	16
Std.e.	12.4	18.8	15.2	28.6	14.8	17.1	17.7	18.0	22.5	16.8	33.9	10.2	22.2	30.3	16.0	19.2		
p-values	2E-09	4E-12	5E-09	8E-08	3E-06	7E-02	8E-17	4E-04	5E-06	5E-01	2E-03	6E-02	9E-02	4E-04	7E-01	3E-02		
Veneto																		
Coeff.	24.4	-30.6	-23.2	9.4	-8.4	-3.9	30.0	-1.5	3.7	10.2	-11.0	3.4	3.2	11.1	-9.8	-4.4	2E-65	14
Std.e.	3.5	4.6	3.5	8.9	4.1	4.5	3.9	6.1	5.1	5.0	9.3	4.1	5.0	8.4	5.3	4.8		
p-values	9E-11	5E-10	3E-10	3E-01	4E-02	4E-01	2E-12	8E-01	5E-01	4E-02	2E-01	4E-01	5E-01	2E-01	7E-02	4E-01		
Friuli Venezia Giulia																		
Coeff.	20.9	-27.9	-18.3	9.0	-9.5	-3.7	24.0	-2.3	7.3	6.4	-4.6	1.8	4.5	9.2	-12.8	-1.1	1E-46	14
Std.e.	4.4	5.7	4.5	9.3	4.6	4.7	5.3	6.8	5.9	3.7	9.7	3.2	5.0	8.7	4.5	4.8		
p-values	4E-06	2E-06	8E-05	3E-01	4E-02	4E-01	1E-05	7E-01	2E-01	8E-02	6E-01	6E-01	4E-01	3E-01	5E-03	8E-01		
Emilia Romagna																		
Coeff.	43.5	-44.0	-25.9	-3.5	-22.4	-28.2	29.6	-10.3	12.6	23.8	4.9	-4.9	8.8	28.6	-6.0	16.1	9E-60	14
Std.e.	6.7	9.2	7.3	10.6	7.6	8.2	7.2	7.4	9.8	9.3	11.5	5.5	10.9	10.6	9.4	10.2		
p-values	1E-09	4E-06	5E-04	7E-01	4E-03	8E-04	6E-05	2E-01	2E-01	1E-02	7E-01	4E-01	4E-01	8E-03	5E-01	1E-01		

p_F: ANOVA p-values of the model; Coeff.: coefficient; Std.e.: standard error

Supp. Table 1b

14 November - 31 December 2020: "confined/autumn period": detailed regression coefficients and relevant standard deviations (Std.e.) and p-values of t-test for the comparison with the null value

	Intercept	T	S	P	U	W	S-T	T-P	T-U	W-T	S-P	S-U	W-S	P-U	W-P	W-U	p _F	Lag days
Val d'Aosta																		
Coeff.	116.2	42.1	-175.1	-27.9	-72.8	-3.7	115.9	13.2	34.4	-183.2	-29.2	90.7	266.3	71.9	-58.5	3.6	1E-10	17
Std.e.	52.1	57.0	87.5	39.9	45.1	76.0	51.8	55.7	46.6	97.5	79.2	57.1	115.8	29.1	36.7	61.9		
p-values	3E-02	5E-01	5E-02	5E-01	1E-01	1E+00	3E-02	8E-01	5E-01	7E-02	7E-01	1E-01	3E-02	2E-02	1E-01	1E+00		
Piemonte																		
Coeff.	74.2	-9.8	16.7	18.4	1.5	-15.6	32.5	10.1	57.8	-3.5	-32.7	-26.8	27.3	-23.1	8.1	-13.8	1E-17	20
Std.e.	22.8	20.1	30.1	30.8	21.5	22.6	18.5	13.5	18.7	17.8	26.8	25.6	24.2	28.3	14.9	20.0		
p-values	3E-03	6E-01	6E-01	6E-01	9E-01	5E-01	9E-02	5E-01	4E-03	8E-01	2E-01	3E-01	3E-01	4E-01	6E-01	5E-01		
Lombardia																		
Coeff.	-23.6	37.7	65.1	25.5	66.7	34.7	-2.3	1.8	21.2	-40.4	-13.3	-55.3	25.1	-23.5	-16.1	-40.2	3E-18	20
Std.e.	23.8	18.9	25.3	33.6	26.2	25.0	17.1	11.6	17.6	21.0	29.1	17.5	32.9	35.6	14.0	27.0		
p-values	3E-01	5E-02	1E-02	5E-01	2E-02	2E-01	9E-01	9E-01	2E-01	6E-02	7E-01	3E-03	5E-01	5E-01	3E-01	1E-01		
Trento																		
Coeff.	100.9	-6.6	-34.3	-3.1	-43.2	9.3	9.2	16.6	3.7	-8.8	-0.8	48.4	-7.8	-2.4	-5.6	-0.3	2E-08	19
Std.e.	20.8	13.8	25.5	17.4	28.1	21.7	14.8	14.2	14.5	12.3	18.0	15.7	24.3	23.6	9.6	29.0		
p-values	3E-05	6E-01	2E-01	9E-01	1E-01	7E-01	5E-01	3E-01	8E-01	5E-01	1E+00	4E-03	8E-01	9E-01	6E-01	1E+00		
Bolzano																		
Coeff.	122.3	49.2	-27.4	-127.2	-173.6	-98.4	-16.1	21.5	40.3	-17.8	-0.3	58.3	93.2	216.1	-35.0	140.0	2E-16	18
Std.e.	41.4	45.7	45.1	36.7	49.2	51.4	33.6	45.7	45.5	32.5	49.5	32.2	52.4	46.3	24.4	58.9		
p-values	6E-03	3E-01	5E-01	2E-03	1E-03	6E-02	6E-01	6E-01	4E-01	6E-01	1E+00	8E-02	8E-02	5E-05	2E-01	2E-02		
Veneto																		
Coeff.	41.8	29.7	9.3	1.6	13.0	11.0	-24.1	4.5	-34.8	-7.7	1.1	-3.3	-10.1	-2.2	2.5	-6.0	3E-11	19
Std.e.	8.9	7.4	7.6	10.6	10.7	12.1	6.8	6.3	7.1	6.8	6.7	8.1	10.4	13.4	7.2	14.8		
p-values	5E-05	4E-04	2E-01	9E-01	2E-01	4E-01	1E-03	5E-01	3E-05	3E-01	9E-01	7E-01	3E-01	9E-01	7E-01	7E-01		
Friuli Venezia Giulia																		
Coeff.	23.9	37.9	29.6	19.4	32.9	20.4	-41.9	39.4	-54.2	-19.3	-19.7	-3.0	-6.3	-34.2	-34.7	-4.3	2E-08	21
Std.e.	15.1	15.6	18.0	23.9	18.2	18.6	9.7	17.4	11.6	21.7	21.5	11.7	21.3	25.3	19.9	23.2		
p-values	1E-01	2E-02	1E-01	4E-01	8E-02	3E-01	1E-04	3E-02	5E-05	4E-01	4E-01	8E-01	8E-01	2E-01	9E-02	9E-01		
Emilia Romagna																		
Coeff.	58.7	26.2	-0.6	1.2	0.1	1.9	-27.1	15.1	-26.7	-20.8	-3.8	13.0	11.8	-4.0	3.4	5.1	4E-05	21
Std.e.	9.6	11.4	9.6	13.9	10.2	10.4	9.1	6.1	10.7	13.8	10.3	8.3	14.6	13.1	15.2	14.0		
p-values	8E-07	3E-02	9E-01	9E-01	1E+00	9E-01	5E-03	2E-02	2E-02	1E-01	7E-01	1E-01	4E-01	8E-01	8E-01	7E-01		

p_F: ANOVA p-values of the model; Coeff.: coefficient; Std.e.: standard error

Supp. Table 2

Annual median values of PM 2.5 ($\mu\text{g}/\text{m}^3$) from 2009 to 2018 (van Donkelaar et al., 2019; Hammer et al., 2020). The target guideline values by WHO are reported too (WHO, 2021)

Lombardia	20.55
Veneto	19.69
Emilia-Romagna	16.96
Piemonte	16.73
Friuli Venezia Giulia	15.22
Trento	14.58
Bolzano	10.61
Val d'Aosta	8.46

Data from: <https://sites.wustl.edu/acag/datasets/surface-pm2-5/#V4.EU.03>

WHO air quality guidelines	5.00
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