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Environmental, climatic, socio-economic factors and non-pharmacological interventions: A comprehensive four-domain risk assessment of COVID-19 hospitalization and death in Northern Italy

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Up to now, studies on environmental, climatic, socio-economic factors, and non-pharmacological interventions (NPI) show diverse associations, often contrasting, with COVID-19 spread or severity. Most studies used large-scale, aggregated data, with limited adjustment for individual factors, most of them focused on viral spread than severe outcomes. Moreover, evidence simultaneously evaluating variables belonging to different exposure domains is scarce, and none analysing their collective impact on an individual level.
Methods: Our population-based retrospective cohort study aimed to assess the comprehensive role played by exposure variables belonging to four different domains, environmental, climatic, socio-economic, and non-pharmacological interventions (NPI), on individual COVID-19-related risk of hospitalization and death, analysing data from all patients (no. 68472) tested positive to a SARS-CoV-2 swab in Modena Province (Northern Italy) between February 2020 and August 2021.
Using adjusted Cox proportional hazard models, we estimated the risk of severe COVID-19 outcomes, investigating dose-response relationships through restricted cubic spline modelling for hazard ratios.
Results: Several significant associations emerged: long-term exposure to air pollutants (NO_2, PM_{10}, $PM_{2.5}$) was linked to hospitalization risk in a complex way and showed an increased risk for death; while humidity was inversely associated; temperature showed a U-shaped risk; wind speed showed a linear association with both outcomes. Precipitation increased hospitalization risk but decreased mortality. Socio-economic and NPI indices showed clear linear associations, respectively negative and positive, with both outcomes.
Conclusions: Our findings offer insights for evidence-based policy decisions, improving precision healthcare practices, and safeguarding public health in future pandemics. Refinement of pandemic response plans by healthcare authorities could benefit significantly.

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1. Introduction

Over the past four years, we have witnessed the spread of SARS-CoV-2 and the resulting pandemic, characterized as one of the most serious global socio-health emergencies since the last century, with profound socio-economic and public health consequences (Bambra et al., 2020; Fonseca and Azevedo, 2020; Miyah et al., 2022; Naseer et al., 2023).

Scientists and researchers worldwide have often questioned the various factors influencing the spread of the virus, conducting large-scale investigations into meteorological, socio-economic, and demographic factors and their effects on COVID-19 related outcomes such as hospitalizations and deaths (Barceló and Saez, 2021; Vandelli et al., 2024; Wachtler et al., 2020; Weaver et al., 2022). Recent studies have identified many factors among which temperature, humidity, air pollution, and UV radiation were the most influential. However, they failed to clearly define the size and contribution of these factors (Ford et al., 2022; Hao et al., 2024). Many inconsistencies in results can be observed across different studies (Balboni et al., 2023; Jerrett et al., 2023). These discrepancies may be determined by actual differences in the effect played by the same factor in different local contexts or could depend on the scale considered and the seasonality, however, they may be as well the result of different methodological weaknesses, such as the absence of control for other influencing or confounding factors or the use of aggregated data (Barceló and Saez, 2021; Nottmeyer et al., 2022).

Considering socio-economic factors, various studies have analyzed worldwide the influence of individual factors, as well as factors related to the socio-economic context showing that COVID-19 had a higher toll on socially disadvantaged populations (Duhon et al., 2021; Lippi et al., 2020). On the other hand, non-pharmacological interventions (NPI) that governments have implemented at the national and local levels have shown to play an important role in containing the spread of the virus. The adoption of these measures, however, has had a varying impact, still under study, due to the implementation of a wide range of interventions differing greatly in timing and strength (Gianino et al., 2021; Mateo-Urdiales et al., 2021).

Further, most studies are often large-scale investigations, frequently based on aggregated data with partial or absent adjustment by sex and age (Bartolomeo et al., 2022; Filippini et al., 2021) and, therefore, many reviews claim the need to investigate exposure at individual level to implement precision based public health interventions. Moreover available studies typically refer prevalently to the first pandemic phase (spring 2020) when testing and data flow were not yet standardized and explore mainly SARS-CoV-2 spread rather than disease severity (Gianino et al., 2021; Vandelli et al., 2024). Finally, literature investigating simultaneously variables related to different exposure domains (such as environmental and climatic factors, individual and socio-economic characteristics, and NPIs) is scarce and to the best of our knowledge no studies investigated the overall concurrent impact of all these factors at an individual level.

Since the very beginning, Italy has been one of the most affected European countries, recording its first case on February 21, 2020, and with a toll of over 26 million infections and 196 thousand related deaths to date (Ministry of Health, 2024). The Province of Modena (Emilia-Romagna, Northern Italy) was one of the most heavily hit by the first pandemic waves, counting over 320,0000 cases over approximately 700,000 inhabitants up to March 2024 (Protezione Civile, 2024). Several authors have investigated this or nearby areas, yet in most cases, studies were carried out on specific subpopulations (Djuric et al., 2022; Mangone et al., 2023; Paduano et al., 2021, Paduano et al., 2023b; Serafini et al., 2023; Sileo et al., 2023; Ugolini et al., 2023), or, using aggregated data (Caranci et al., 2021; Gandolfi et al., 2021; Vinceti et al., 2021a, 2021b) or focusing on a specific factor or domain (Ferroni et al., 2020; Giorgi Rossi, 2020).

The purpose of this study was to investigate the overall and comprehensive effect of several exposure variables belonging to different exposure domains (environmental, climatic, socio-economic factors, and non-pharmacological interventions) on the individual risk of COVID-19 related hospitalization and death, during the first three waves in the specific context of the Province of Modena.

2. Methods

2.1. Study design

This is a population-based, retrospective cohort study. The cohort included all subjects (no. 68472) living in the province of Modena who tested positive to a SARS-CoV-2 real-time polymerase chain reaction rhino-pharyngeal swab performed between February 21, 2020 (first local diagnosed case) and August 30, 2021. The investigated period included the first three pandemic waves occurred in Italy according to data from National Institute of Health (Stafoggia et al., 2023). The study was approved by the Ethics Committee of the Area Vasta Emilia Nord (study protocol no. AOU 0028505/21 approved on September 23, 2021) and was carried out in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

2.2. Study population

Data on subjects were provided by the Local Health Authority (LHA) of Modena (Emilia-Romagna, Northern Italy). During the pandemic the Public Health Service of the LHA, through the Active Surveillance and Isolation program (SAI), collected on a daily based data on suspected and confirmed cases as well as their contacts, encompassing the handling of isolation measures, quarantine, diagnostic and follow-up testing, and the ongoing surveillance of individual cases.

For each individual the following anonymized information was extracted: age (in years), sex and residence census area (using as reference the 2011 Population National Census data, (ISTAT - Italian Institute of Statistics, 2024)), time (week) and length of positivity, symptoms and outcome (hospitalization/death). We queried vaccination status as well and found only 3184 members of our cohort were vaccinated prior to the positive swab; thus about 95% of the cohort was unvaccinated during the study period (Paduano et al., 2023a).

2.3. Setting

The Province of Modena is situated in the Emilia-Romagna region, Northern Italy, and spans over 2500 km^2, with a population exceeding 700,000 individuals (average population density of 261 inhabitants/km^2). Modena itself is a mid-sized city, while the province comprises a combination of urban centers and rural areas. In terms of demographic composition, the province exhibits significant variations based on factors such as age, sex, ethnicity, educational attainment, and employment. Geographically, the area can be described as a diverse territory extending from the Apennine mountains, reaching an altitude of up to 2165 m above sea level, to the Po Valley (8 m) (Province of Modena, 2021).

2.4. Outcomes

The primary outcomes were COVID-19 related hospitalizations (yes/no) and COVID-19 related deaths (yes/no). Time-to-event for each outcome was available and was calculated from positivity to outcome or swab negativization. Events occurring until October 24, 2021, were included. Due to data protection issues, time-to-event was calculated referring to the week in which the event occurred.

2.5. Exposure domains and variables

Information on different exposure variables were extracted from different data sources, specifically processed and integrated, and then linked to the cohort dataset.

2.5.1. Environmental long-term exposure domain

Data pertaining to long-term air pollution was retrieved from the Regional Agency for Prevention, Environment, and Energy of the Emilia-Romagna Region (ARPAE - Regional Agency for Prevention, Environment, and Energy of the Emilia-Romagna Region, 2023). Extracted data includes particulate matter with aerodynamic diameter <10 and < 2.5 μm (PM_{10} and $PM_{2.5}$ respectively) (expressed in μg/m^3); nitrogen dioxide NO_2 measured as annual mean concentrations at ground level (expressed in μg/m^3), and ozone (O_3) as expressed as the yearly number of days exceeding the threshold value of 120 μg/m^3. Air pollution data was available in ASCII raster format as a grid with a resolution of 3 km × 3 km for the years 2016, 2017, 2018, and 2019. Data was processed and averaged to obtain an estimate of long-term exposure for the years 2016–2019 for each subject's census tract and then linked to our cohort dataset. The average over the previous four years was chosen according to availability of data unaffected by the pandemic (e.g. prior lockdown and limitation of people movements) and previous literature on the topic (Ranzi et al., 2023; Stafoggia et al., 2020, 2023). More details on environmental variables may be found in Supplementary Material.

2.5.2. Climatic short-term exposure domain

Concerning climatic data, we retrieved hourly average temperature at 2 m (Celsius degrees), hourly cumulated precipitations (mm), average wind speed (m/s) and direction (degrees) at 10 m, relative humidity (percentages), hourly potential evapotranspiration (mm) according to Penman-Monteith (Monteith, 1965; Penman, 1948), hourly average global radiation flux at 2 m (W/m^2) for the period January 2020–August 2021. This data was obtained from the daily high-resolution ERG5 gridded meteorological dataset, developed by the Hydro-Meteorological-Climate Structure of Regional Agency for Prevention, Environment, and Energy (ARPAE-SIMC) of the Emilia-Romagna Region. ERG5 data has been provided since 2001 by interpolating hourly measurements from weather stations for the main meteorological variables onto a 5 km × 5 km grid that covers the Emilia-Romagna Region (Antolini et al., 2016). Data was then processed to obtain weekly averages for each subject's census tract and then linked to the cohort dataset. More details on climatic variables may be found in Supplementary Material.

2.5.3. Socio-economic exposure domain

To assess the socio-economic context, we used the Italian Deprivation Index (DI) at the census section level, calculated on 2011 census data (the most recent available) and commonly used in the assessment of deprivation in Italy (Bartolomeo et al., 2022; Rosano et al., 2020; Fortunato et al., 2023; Mateo-Urdiales et al., 2021).

The Italian DI is mainly used as a proxy of social disadvantage, especially when such data at the individual level are difficult to access or unavailable, and the higher the score, the higher is the social disadvantage (Bartolomeo et al., 2022).

The values of the Italian Deprivation Index (DI) per census area were extracted from the Emilia-Romagna Region website and then linked to the cohort dataset. More details on Italian DI may be found in Supplementary Material.

2.5.4. Non-pharmacological interventions (NPI) exposure domain

Italy, and the Province of Modena, as many other countries, have responded by implementing non pharmaceutical interventions (NPI) which include school and workplace closures, cancellation of public events and gatherings, stay-at-home orders, and international and domestic travel restriction (Duhon et al., 2021).

Restrictive measures were analyzed calculating the Stringency Index (SI) and Containment and Health Index (CHI), as proposed by the Oxford COVID-19 Government Response Tracker (Hale et al., 2021). The SI is a composite index based on eight social measures: school closure, workplace closure, cancellation of public events, restrictions on gatherings, public transport closure, stay at home requirement, restrictions on internal movements, international travel controls. The CHI is a composite index based on the same eight social measures and six other public health interventions. The six public health interventions are: public information campaigns, testing policies, contact tracing, facial coverings, vaccination policies, protection of elderly people.

The index on any given day is calculated as the mean score of the specific metrics, each taking a value between 0 and 1. A higher score indicates a stricter response (i.e. 1 = strictest response)

To calculate the values of both Indexes in the Province of Modena, we analyzed 135 regulations issued at both the national and local level, resulting in 62 distinct scores over the course of period under consideration. Single daily CHI and SI values were then averaged to obtain weekly values, that were then merged with the dataset with individual data. More details on non-pharmacological interventions may be found in Supplementary Material.

2.6. Spatial frames and time lag

For addressing the spatial frame, we were able to collect data with a minimal spatial resolution up to the census tract of subjects' home for environmental, climatic, and socio-economic variables. NPI variables were homogeneous across the province of Modena, changing only according to time.

Considering the timeframe, due to data-protection constrictions we were able to obtain for each subject the weeks referring to first positivity and health outcomes. Time to event for survival analysis as well as lag time were therefore calculated using weeks as temporal unit. In order to estimate the correct exposure at time of infection, as suggested by existing literature, we defined different specific lag time between each variable exposure and week of swab positivity. For short-term climatic exposure, we considered a lag time of 2 weeks based on a 7-day incubation period (Wu et al., 2022) and the mean delay between onset of symptoms and swab outcome, estimated to be 5 and 3 days, respectively, in the first and second pandemic wave (ISS - Italian National Institute of Health, 2020). For NPI's lag time, we considered a lag time of 3 weeks, based on the average time required for restrictions to have an impact on SARS-CoV-2 incidence in Italy during the first waves (Guzzetta et al., 2021).

2.7. Statistical methods

Quantitative variables were summarized in the main manuscript using median and interquartile range. For full descriptive statistics, please refer to Supplementary Material. Qualitative variables were summarized by absolute and relative frequencies.

To investigate the role played by factors and exposure variables belonging to different domains on the risk of hospitalization or death for COVID-19 we used a Cox proportional hazard model with adjustment of potential confounders.

The Cox model estimated the instantaneous hazard of a health outcome (hospitalization or death) during the follow-up as:

$$h_{ij}(t) = h_0(t)^{\left(X_{ij}+E_{ij}+C_{itj}+S_{ij}+N_{itj}\right)} \quad \text{Equation 1}$$

where.

$h_{ij}(t)$ = hazard function for the *i*th subject in the *j*th census tract neighborhood;
$h_0(t)$ = baseline hazard;
X_{ij} = individual risk factors (sex and age) for individual *i;*

Table 1
Main socio-demographic characteristics and exposure levels of infected subjects Data is reported for the overall cohort and for subjects stratified by outcome (hospitalization or death). Continuous data are shown as median (interquartile range), categorical data as number (percentage) (Province of Modena, Italy, 2020–2021). Pollutants are expressed in μg/m^3, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2, Italian Deprivation Index (DI) in quintiles and Containment and Health Index (CHI) and Stringency Index (SI) in relative frequencies (1 equal to the highest level of restriction).

Characteristics	Overall	Hospitalized		Died	
	N = 68472	no, N = 62119	yes, N = 6353	no, N = 66740	yes, N = 1732
Sex					
M	34348 (50.2%)	30659 (49.4%)	3691 (58.1%)	33377 (50.0%)	971 (56.1%)
F	34124 (49.8%)	31460 (50.6%)	2662 (41.9%)	33363 (50.0%)	761 (43.9%)
Age (y)	43.00 (24.00, 57.00)	40.00 (23.00, 54.00)	71.00 (57.00, 81,00)	42.00 (24.00, 56.00)	84.00 (77.00, 90.00)
Unknown	1	1	0	0	1
A – Environmental domain					
NO_2	24.30 (19.65, 28.00)	24.30 (19.65, 28.00)	24.18 (18.71, 27.82)	24.30 (19.65, 28.00)	23.71 (17.69, 28.00)
Unknown	3358	3224	134	3309	49
$PM_{2.5}$	20.06 (18.75, 20.62)	20.06 (18.75, 20.62)	20.04 (18.74, 20.62)	20.06 (18.75, 20.62)	20.06 (18.23, 20.68)
Unknown	3358	3224	134	3309	49
PM_{10}	29.75 (28.55, 31.14)	29.76 (28.55, 31.14)	29.71 (28.41, 31.14)	29.75 (28.55, 31.14)	29.77 (28.20, 31.26)
Unknown	3358	3224	134	3309	49
B – Climatic Domain					
Minimum Temperature	3.92 (1.18, 8.34)	3.96 (1.17, 8.39)	3.53 (1.21, 7.07)	3.93 (1.17, 8.36)	3.71 (1.61, 6.93)
Unknown	3358	3224	134	3309	49
Total Precipitation	0.37 (0.03, 2.00)	0.37 (0.03, 2.00)	0.33 (0.03, 1.96)	0.37 (0.03, 2.00)	0.41 (0.50, 2.05)
Unknown	3358	3224	134	3309	49
Wind speed	1.47 (1.13, 1.75)	1.46 (1.13, 1.74)	1.52 (1.20, 1.87)	1.47 (1.13, 1.75)	1.51 (1.18, 1.94)
Unknown	3358	3224	134	3309	49
Relative humidity	77.65 (66.16, 86.50)	77.80 (66.28, 86.62)	76.15 (65.36, 85.72)	77.64 (66.14, 86.50)	77.85 (66.64, 86.05)
Unknown	3358	3224	134		
Radiation	106.97 (61.86, 158.24)	106.54 (61.84, 158.32)	111.03 (68.49, 157.89)	106.91 (61.86, 158.39)	109.25 (61.09, 152.10)
Unknown	3358	3224	134	3309	49
C – Socio-economic domain					
Italian Deprivation Index (DI)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)
Unknown	3910	3710	200	3805	105
D – Non-pharmacological domain					
Stringency Index (SI)	0.66 (0.58, 0.74)	0.66 (0.58, 0.74)	0.67 (0.58, 0.74)	0.66 (0.58, 0.74)	0.67 (0.58, 0.74)
Containment and Health Index (CHI)	0.74 (0.63, 0.80)	0.74 (0.63, 0.80)	0.74 (0.64, 0.80)	0.74 (0.63, 0.80)	0.69 (0.64, 0.75)
C1 - School closure	0.50 (0.17, 0.71)	0.50 (0.17, 0.71)	0.50 (0.21, 0.83)	0.50 (0.17, 0.71)	0.50 (0.21, 0.93)
C2 - Workplace closure	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)	0.50 (0.50, 0.67)
C3 - Cancellation public events	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
C4 - Restrictions on gatherings	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.88, 1.00)
C5 - Public transport closure	0.50 (0.50, 0.50)	0.50 (0.50, 0.50)	0.50 (0.36, 0.50)	0.50 (0.50, 0.50)	0.50 (0.00, 0.50)
C6 - Stay at home requirements	0.50 (0.00, 0.50)	0.50 (0.00, 0.50)	0.50 (0.21, 0.50)	0.50 (0.00, 0.50)	0.50 (0.00, 0.50)
C7 - Restrictions on internal movement	0.32 (0.00, 0.75)	0.32 (0.00, 0.75)	0.32 (0.25, 0.75)	0.32 (0.00, 0.75)	0.32 (0.00, 0.75)
C8 - International travel controls	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)	0.88 (0.88, 0.88)
H1 - Public information campaigns	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
H2 - Testing policy	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)	0.67 (0.67, 1.00)
H3 - Contact tracing	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
H6 - Facial coverings	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (0.93, 1.00)	1.00 (1.00, 1.00)	1.00 (0.25, 1.00)
H7 - Vaccination policy	0.60 (0.00, 0.60)	0.60 (0.00, 0.60)	0.00 (0.00, 0.60)	0.60 (0.00, 0.60)	0.00 (0.00, 0.60)
H8 - Protection of elderly people	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

E_{ij} = long-term environmental exposure core variables for the individual *i* in census tract *j*;
C_{itj} = climatic exposure core variables for the individual *i* in census tract *j* at the time of infection *t*;
S_{ij} = socio-economic exposure core variable for the individual *i* in census tract *j*;
N_{itj} = non-pharmacological intervention core variable for the individual *i* in census tract *j* at the time of infection *t*.

Equation (1) represents the general form of the model. To assess the role played by different exposure variables and different exposure domains we built different models. Firstly, for each exposure variable we ran separate unadjusted models and models adjusted only for individual risk factors (age and sex). Then, we set up four independent models, one for each exposure domain (environmental, climatic, socio-economic, NPI). To adjust each domain model for the potential confounding effect of variables belonging to the other exposure domains, we selected core variables for each exposure domain according to the following steps. For socio-economic and NPI domains, we used respectively Italian DI and CHI as these indexes represent a composite measure for their domains. For identifying the composite measure for the environmental or climate domain, we performed a principal component analysis (PCA) of standardized variables in each domain and we selected the minimum number of components explaining at least a percentage of variability equal to 0.95p, where p is the number of variables in each domain (Kleinbaum and Klein, 2012; *Principal Component Analysis*, 2002).

Each of the four independent models was run for each variable of an exposure domain, adjusting it, as shown in eq. (1), for the individual risk factor and the exposure core variables of the other exposure domains. The model frames were as follows:

Model A.x (environmental domain assessing of environmental variable x) was adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.

Model B.y (climatic domain assessing climatic variable y) was adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.

Model C.z (socio-economic domain assessing socio-economic variable z) was adjusted for age, sex, PCA environmental factor scores, PCA

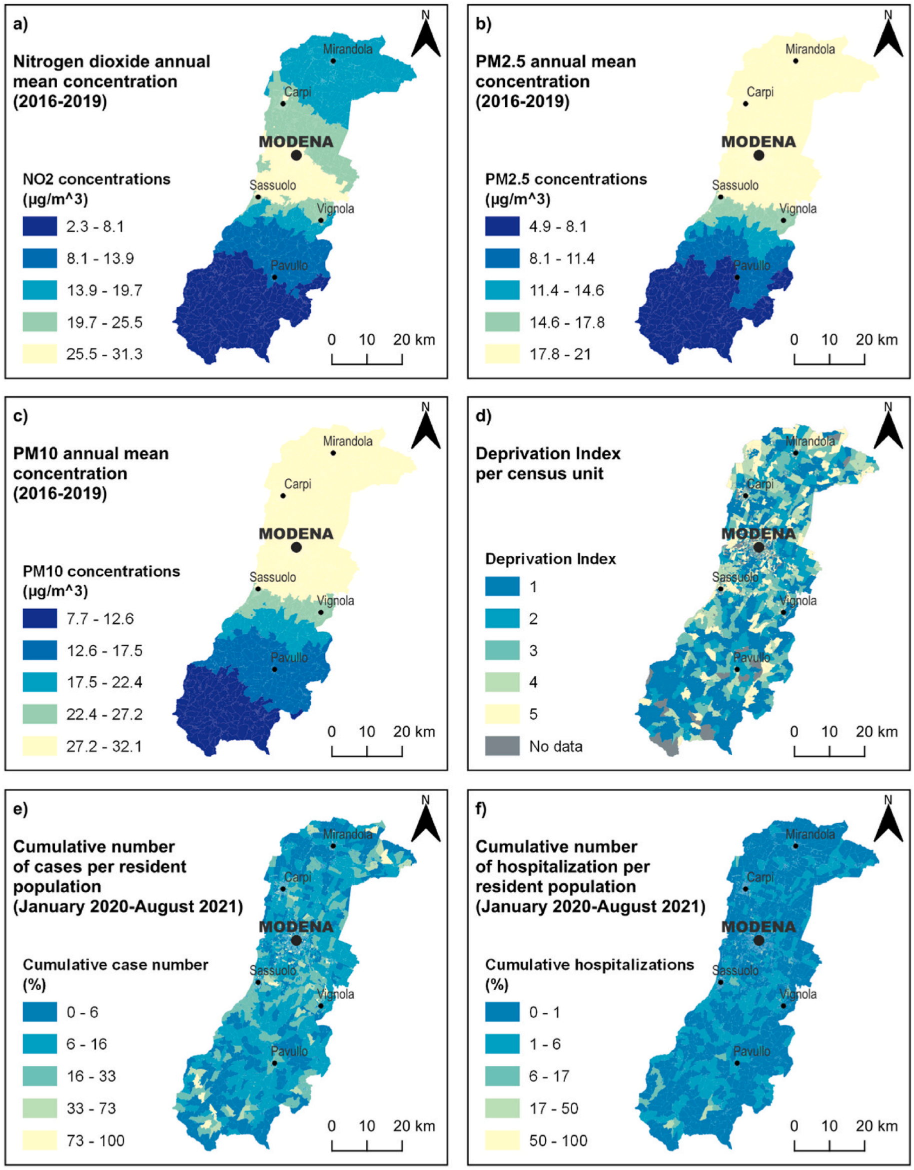

Fig. 1. Spatial distribution time-invariant factors considered for the Province of Modena: a) NO_2 annual mean concentration averaged over 2016–2019 (μg/m^3); b) $PM_{2.5}$ annual mean concentration averaged over 2016–2019 (μg/m^3); c) PM_{10} annual mean concentration averaging over the period 2016–2019 (μg/m^3); d) Italian Deprivation Index (Rosano et al., 2020) per census unit; e) cumulative number of COVID-19 cases per resident population per census unit for the investigated period (January 2020–August 2021); f) cumulative number of COVID-19 cases per resident population per census unit (for the investigated period (January 2020–August 2021).

Data clustering in maps a), b) and c) is based on equal interval mode, while in maps e) and f), classification follows Jenks natural breaks method.

climate factor scores and CHI index.

Model D.w (NPI domain assessing NPI variable w) was adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and deprivation index.

Finally, we explored the dose-response functions for each exposure variable by producing restricted cubic splines. Restricted cubic splines were calculated using 4 knots (5th, 35th, 65th, 95th percentile) and using the median as reference for each exposure variable. To assess the impact of outliers on our curves, we ran a sensitivity analysis eliminating data below the 2.5 and above 97.5 percentile.

The most relevant findings are shown in the main text while the results of all statistical analyses carried out may be found in Supplementary Material.

We used Excel (Microsoft, Redmond, WA, USA) and R (R Core Team version 4.3.1 (2023), Vienna, Austria (R Project, 2023)) for descriptive statistics, plotting and advanced statistical analysis, with packages including tidyverse, survival functions and using the rcs function of the rms and plotHR to create spline curves.

This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Vandenbroucke et al., 2007).

3. Results

Table 1 and corresponding Table A in Supplementary Material, displays the main features and the individual exposure distribution of the cohort of the 68472 patients (median age: 43 years; 50.2% males), who were infected by SARS-CoV-2 from the beginning of the pandemic (February 20, 2020) to August 31, 2021, of whom 6353 (9%) were hospitalized and 1732 (3%) died.

Fig. 1 shows the spatial distribution for long-term exposure variables and cumulative number of cases and hospitalizations per residents in the

Table 2
Results of adjusted Cox proportional hazard model for COVID-19 related hospitalization and death (Province of Modena, Italy, 2020–2021). aHR: adjusted Hazard Ratios. aHR calculated for each increment of 1 unit.
Pollutants are expressed in μg/m^3, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2, Italian Deprivation Index (DI) in quintiles and Containment and Health Index (CHI) and Stringency Index (SI) in relative frequencies (1 equal to the highest level of restriction).

	Hospitalization	Death
	aHR (95%CI)	aHR (95%CI)
A - Environmental domain[a]		
NO_2	1.0047 (1.0006–1.0087)	1.0020 (0.9947–1.0093)
PM_{10}	1.0058 (1.0004–1.0113)	1.0071 (0.9972–1.0170)
$PM_{2.5}$	1.0059 (0.9989–1.0130)	1.0088 (0.9960–1.0219)
B - Climatic domain[b]		
Minimum temperature	0.9747 (0.9678–0.9816)	0.9653 (0.9530–0.9778)
Total precipitation	0.9823 (0.9724–0.9922)	0.9948 (0.9773–1.0125)
Wind speed	1.3898 (1.3251–1.4577)	1.4098 (1.2950–1.5348)
Relative humidity	0.9835 (0.9814–0.9856)	0.9874 (0.9834–0.9914)
Radiation	1.0024 (1.0020–1.0027)	1.0013 (1.0005–1.0021)
C- Socio-economic domain[c]		
Italian Deprivation Index (DI)	1.0413 (1.0223–1.0606)	1.0650 (1.0292–1.1020)
D - Non-pharmacological domain[d]		
Stringency Index (SI)	0.3833 (0.2887–0.5089)	0.2066 (0.1290–0.3310)
Containment and Health Index (CHI)	0.1712 (0.1265–0.2317)	0.0554 (0.0359–0.0857)
C1 - School closure	1.1970 (1.0909–1.3135)	1.8778 (1.5821–2.2289)
C2 - Workplace closure	0.6697 (0.5750–0.7801)	0.5326 (0.4120–0.6884)
C3 - Cancellation public events	0.7025 (0.5971–0.8266)	0.5889 (0.4337–0.7997)
C4 - Restrictions on gatherings	0.8646 (0.7305–1.0232)	0.5830 (0.4253–0.7993)
C5 - Public transport closure	0.2970 (0.2530–0.3487)	0.1144 (0.0871–0.1503)
C6 - Stay at home requirements	0.8322 (0.7159–0.9673)	0.4692 (0.3609–0.6098)
C7 - Restrictions on internal movement	0.8625 (0.7792–0.9546)	0.7533 (0.6273–0.9046)
C8 - International travel controls	0.8575 (0.5279–1.3927)	0.7751 (0.3131–1.9187)
H1 - Public information campaigns	0.1974 (0.1610–0.2421)	0.1591 (0.1180–0.2145)
H2 - Testing policy	0.4738 (0.3910–0.5742)	0.1344 (0.0968–0.1866)
H3 - Contact tracing	0.2343 (0.1593–0.3446)	0.3958 (0.1878–0.8338)
H6 - Facial coverings	0.4093 (0.3662–0.4575)	0.2204 (0.1834–0.2648)
H7 - Vaccination policy	0.7197 (0.6492–0.7979)	0.3354 (0.2747–0.4095)
H8 - Protection of elderly people	0.2343 (0.1593–0.3446)	0.3958 (0.1878–0.8338)

[a] Model adjusted for age, sex, PCA climate factor scores, deprivation index and CHI index.
[b] Model adjusted for age, sex, PCA environmental factor scores, deprivation index and CHI index.
[c] Model adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and CHI index.
[d] Model adjusted for age, sex, PCA environmental factor scores, PCA climate factor scores and deprivation index.

Province of Modena. Significant geographical differences in air pollution exposure levels can be observed across the investigated area as well as in Italian DI and in the outcomes of interest.

The results of adjusted Cox proportional hazard models are shown in Table 2 and corresponding Table B in Supplementary Material. After adjusting for many confounders, several variables show a significative effect on COVID-19 hospitalization. More specifically an increasing risk is highlighted for all air pollutants, while a negative trend can be observed for all the climatic variables except for wind speed and UV radiation. Increasing socio-economic deprivation appears significantly associated with a higher risk of hospitalization while all non-pharmacological interventions, excluding school closure, reduce the risk of hospitalization. Among them, public health interventions seem to have a higher impact on risk reduction than social measures. Similar associations can be observed for COVID-19 related deaths. Tables with all investigated variables as well as unadjusted models may be found in Supplementary Material.

Figs. 2 and 3 show dose-response curves modelled excluding outliers (curves with outliers, as well as curves of other investigated variables not reported in the main text, may be found in Supplementary Material). Where not otherwise specified, hospitalization and death curves appear consistent across exposure variables, as well as with curves with outliers.

Different shapes and relationships can be observed for the investigated variables. Long-term environmental domain variables show complex trends with the risk of hospitalization. All three pollutants present elevated risks at relatively low concentrations, though with significant uncertainty; lower risks at moderate concentrations, followed by higher risks at elevated levels, and then decreasing risks at extremely high concentrations. As for death they show a quasi-linear relationship with the risk increasing with higher exposure levels.

Considering the climatic domain, wind speed shows a positive quasi-linear response curve. Relative humidity shows a steep indirect risk response in the central part of the curve characterized by a particularly narrow confidence interval. Minimum temperature shows an N-shaped curve showing an increased risk at extreme temperatures and this trend remains consistent when analyzing average and maximum temperatures (Supplementary Material). UV radiation shows an inverse U-shaped curve. Precipitation exhibits a direct quasi-linear risk curve that reverses when considering fatalities and outliers.

The Deprivation Index and the Containment and Health Index demonstrate a clear linear association, respectively positive and negative, with the risk of COVID-19-related hospitalizations and deaths. Notably, among NPI, only school closure (Supplementary Material) shows an inverse trend with hospitalization risk showing lower risks at lower levels of restrictions and higher risks of hospitalization with greater restrictions. This trend, however, is not confirmed when the risk of death is evaluated as the curve shows a direct linear trend.

4. Discussion

To the best of our knowledge this is the first study to investigate individual-level risk of severe COVID-19 outcomes comprehensively and simultaneously across four exposure domains (environmental, climatic, socio-economic, and non-pharmacological interventions). By employing time-to-event analysis, we were able to explore the risks of hospitalization and mortality using survival analysis techniques, enabling the estimation of Hazard Ratios for COVID-19-related outcomes with a spatial resolution extending down to the census tract level of the patients' neighborhoods. We focus on the period starting from the local first case occurred in February 2020 and leading up to September 2021 in the Province of Modena, where significant challenges arose due to the COVID-19 pandemic (Serafini et al., 2023; Ugolini et al., 2023). Vaccination coverage was still scarce and therefore our results provide valuable insights on the impact of the several exposures on a highly contagious respiratory virus before implementation of vaccination strategies. After adjusting for several confounding factors, we were able to observe a plethora of factors still able to modify, often with complex relationships, the risk for severe COVID-19 outcomes.

4.1. Main results and literature comparison

4.1.1. Environmental domain

In our study, we observed significant positive associations, although extremely complex, between COVID-19 hospitalization risk and long-term exposure to different air pollutants (NO_2, O_3, PM_{10}, and $PM_{2.5}$). Similar associations were observed for COVID-19-related deaths, with a weaker link for NO_2. Our results are in accordance with previous studies carried out at national level. The extremely high air pollution levels typically recorded in Northern Italy, including the Province of Modena, were identified as an additional co-factor for the region's high lethality (Filippini et al., 2020, 2021). Upper airways defenses can be weakened by chronic exposure to pollutants and this has been hypothesized to facilitate virus penetration in lower airways, especially in colder climate that reduce cilia mobility (Conticini et al., 2020). International evidence also highlighted connections between air pollution and COVID-19 related outcomes (Vandelli et al., 2024). Several studies indicate a positive association between average air pollution levels and mortality from COVID-19, some focusing on individual pollutants, such as $PM_{2.5}$ (Travaglio et al., 2021; Wu et al., 2020), NO_2 (Filippini et al., 2020, 2021; Ogen, 2020), and others identifying a cumulative effect (Jerrett et al., 2023).

4.1.2. Climatic domain

Different climatic factors appeared significantly related to the risk of COVID-19 hospitalization or death in our study, some results were in accordance and others in contrast with previous evidence (Balboni et al., 2023; Isaia et al., 2021; Li et al., 2022).

Humidity showed a steep reduction of risk the higher the percentage, an increased risk was observed both at very low and at very high temperatures, while wind speed showed a positive linear response with COVID-19 related outcomes.

Both humidity and temperature can affect the defense mechanisms of the nasal mucosa promoting therefore a deeper reach of the virus into the airways, which can lead to more severe infections and contribute to a poor prognosis (Kifer et al., 2021; Pramanik et al., 2022; Sera et al., 2021; Weaver et al., 2022; Yang et al., 2021). Temperature and humidity can interfere as well with the size of droplets and their persistence in the air, but the extent to which this would affect severity is not known (Bourdrel et al., 2021).

Wind speed may increase the risk of severe COVID-19 outcomes in different ways. For instance, it can favor immobility of the cilia of the respiratory system if associated with low temperatures and, further, it may modify the distance of virus transmission via droplets, and, as the virus can also be adsorbed on suspended particles that accumulate near the ground, an increase in wind speed is likely to accelerate as well the airborne transmission spread of COVID-19 (Barceló and Saez, 2021; Yang et al., 2021).

Temperature extremes (both hot and cold) may increase the risk of severe COVID-19 outcomes also through complex interactions with social behavior leading the population to prefer enclosed spaces, limiting non artificial air circulation, as it has been observed by some authors (Damette et al., 2021; Nottmeyer et al., 2022).

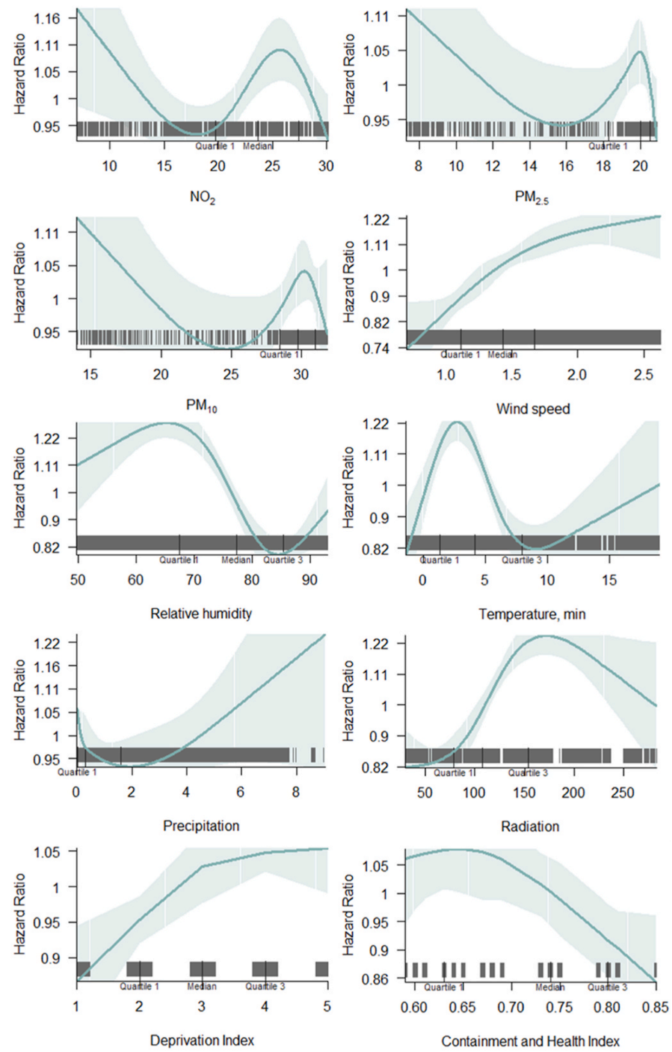

Fig. 2. Dose-response splines for hospitalized patients, excluding outliers. Adjusted Hazard Ratios calculated for each increment of 1 unit. Pollutants are expressed in μg/m^3, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2, Italian DI in quintiles and CHI in relative frequencies (1 equal to the highest level of restriction).

Similar curves have been observed in another COVID-19 survival study (Jerrett et al., 2023). This study, akin to our own work, employs Cox proportional hazards models to assess whether prolonged exposure to air pollution and meteorological conditions at the time of diagnosis influenced the mortality risk in patients with a COVID-19-related disease. Authors observed that temperature exhibited a U-shaped relationship, with higher risks apparent at lower temperatures. Conversely, for most pollutants, linear trends were observed, provided sufficient data was available to support spline derivation. However, other evidence suggests the existence of a correlation between humidity and COVID-19 but shows a role played by humidity changing according to the scale considered and seasonality (Vandelli et al., 2024). Regarding wind speed, some studies found a negative association with COVID-19 cases, but others have reached different conclusions (Vandelli et al., 2024; Yang et al., 2021).

Further, in our study also solar radiation emerged as a factor influencing the risk of hospitalization and death. Once again, previous evidence shows contradictory results, even though several studies suggest that solar radiation may have a protective effect against the development and severity of COVID-19. Our study, on the contrary, highlights

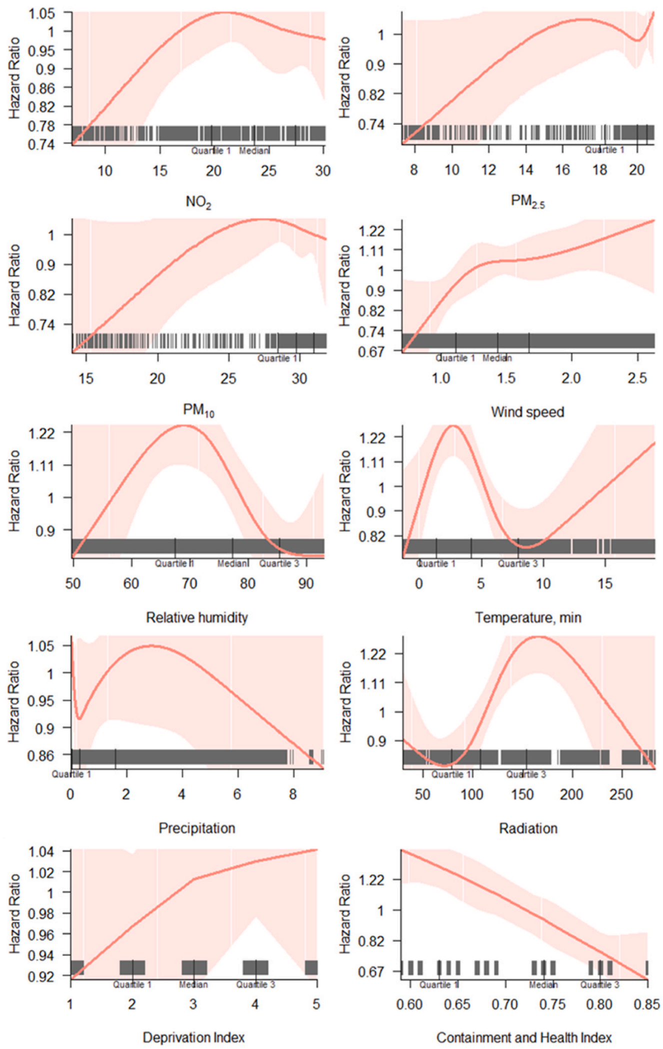

Fig. 3. Dose-response splines for deceased patients, excluding outliers. Adjusted Hazard Ratios calculated for each increment of 1 unit. Pollutants are expressed in μg/m^3, precipitation in mm, temperature in Celsius degrees, wind speed in m/s, relative humidity in percent, solar radiation in W/m^2, Italian DI (median of quintiles) and CHI in relative frequencies (1 equal to the highest level of restriction).

seemingly conflicting results, indicating a potential increased risk of hospitalization associated with higher levels UV rays and a decreased risk of hospitalization only in the presence of the highest level of radiation. While UV radiation seems crucial for viral instability in sun-exposed areas, most of the SARS-CoV-2 transmission occurs indoors, where sunlight's impact on transmission may be limited (Isaia et al., 2021; Qian et al., 2021). To interpret these contradictory findings, it is essential to consider the geographical context, other environmental factors, and human mobility (Moriyama et al., 2020; Vinceti et al., 2022).

Finally, in our study, we observed opposite relationships between precipitation and COVID-19-related hospitalization (indicating an increased risk) and mortality (suggesting a decreased risk). Our hypothesis posits that precipitation may influence social behaviors, potentially leading individuals to favor enclosed spaces. On the other hand, segments of the population, particularly the elderly, who are more susceptible to severe outcomes, might exhibit a tendency to stay at home, thereby reducing their exposure to the virus.

4.1.3. Socio-economic domain

Our results on COVID-19 severity and mortality confirmed higher risks for disadvantaged groups as demonstrated by many other authors (Di Girolamo et al., 2020; Wu et al., 2020). However, literature shows once again inconsistent findings (Wachtler et al., 2020) as UK and US ecological studies found a positive link between deprivation and SARS-CoV-2 outcomes, while other authors found no such association or identified wealthier groups facing higher COVID-19 impact (Mateo-Urdiales et al., 2021).

Considering specific socio-economic features, numerous studies connect both lower education and belonging to a lower social status to more severe outcomes in SARS-CoV-2 infection (Vandelli et al., 2024). We can also hypothesize that higher education may lead to quicker healthcare-seeking behavior, reducing complications and the impact of unrecognized chronic diseases on the infectious clinical picture.

Considering education, employment disparities arise, particularly for low-educated individuals involved in manual jobs for which remote work is impractical, and maintaining safety distances is challenging (Nayak et al., 2020). Further, these jobs often involve exposure to environmental and chemical risks, contributing to increased risks of respiratory diseases, cancers, hypertension and stress, that is chronic conditions known to increase the risk of hospitalization and mortality in COVID-19 infection (Mateo-Urdiales et al., 2021). Inequalities in working conditions therefore likely contribute to the uneven distribution of the COVID-19 disease burden (Gianino et al., 2021). In the Province of Modena, construction companies, metalworking and food industries are prevalent, exposing individuals to extreme temperatures and unfavorable working conditions, increasing vulnerability to respiratory infections.

4.1.4. Non-pharmacological interventions

Evidence on NPI yield conflicting results. Some studies show a relative impact, weaker than climatic and socio-demographic factors (Duhon et al., 2021), while others fail to replicate these conclusions (Wagner et al., 2020). Literature generally agrees on the greater effectiveness of a combination of interventions, changing across time adapting to the evolving epidemiological situation, over a single drastic measure like the long-term lockdown set up in Wuhan (China), and these observations are contradicted only by studies carried out immediately after the first wave, even in Italy (Haug et al., 2020; Meunier, 2020).

Our results align with these findings highlighting how the composite of distinct restrictive social and public health measures exhibits a discernible protective effect concerning both Stringency Index (SI) and Community Health Index (CHI).

Individual measures implemented within the realm of public health appear to have the highest impact on risk reduction, manifesting a protective trend that intensifies with the increasing stringency of implementation. On the other hand, certain measures, particularly those of a social nature, display a more intricate pattern, with an interpretation that is not immediately clear, prompting nuanced reflections.

One possible explanation could link to the prolonged adherence to stringent restrictions that may lead to opposing behaviors, especially in domestic and private settings, thereby potentially diminishing their effectiveness. Additionally, it is essential to acknowledge that these restrictions in Italy entail a complex bureaucratic process for implementation, resulting in a time lag between the observed outcome variations and the execution of subsequent restrictive interventions. Furthermore, Genovese et al. (2022) showed that the Italian population behavior had a general low levels of risk perception and low perception of self-efficacy, especially in the first phase of the pandemic (Genovese et al., 2022).

In particular, in our study, school restrictions show conflicting results, as we observed that lighter forms of restrictions seem effective in reducing COVID-19 outcomes, while stricter restrictions (which in Italy involved complete closure of infant and children's schools) result in an increased risk of hospitalization and death. This increased risk could be explained by the fact that the total closure of schools, which is not paralleled by the cessation of remote work and the lack of support measures for working parents, already burdened the effects of the pandemic (Ferrari et al., 2022; Righi et al., 2024), results in the possibility of relying on grandparents for the daily management of children, especially in those age groups that are not yet self-sufficient. This results in an increased exposure of the most vulnerable segments of the population.

Literature as well shows conflicting evidence on the role played by school activities restrictions. Some studies find school closures more effective than other measures like gathering bans or business closures, considered to have a moderate effect (Brauner et al., 2021) while other authors highlight that in deprived public and private spaces (schools, workplaces, houses) with inadequate ventilation, the risk of infection may be higher (Bartolomeo et al., 2022). Anyhow, most literature studies focus on incidence impact, with fewer addressing hospitalizations and deaths.

Of all the preventive measures, only the vaccination strategy is aimed not only against the infection but also against the severity of the disease. In the province of Modena, vaccination has been available since January 2021 for healthcare workers and extremely fragile subjects, such as immunosuppressed patients and patients residing in healthcare facilities. Starting from the following months, the group of recipients has been gradually expanded based on criteria relating to age, the presence of chronic pathologies and the type of work performed. Despite a very low vaccination rate in these early periods of the pandemic, this measure has indeed shown significant protective effects as it is aimed at subjects at high risk of developing serious infections, in accordance with previous literature (Homan et al., 2022; Lorenzon et al., 2024).

4.2. Limitations and strengths

Our study must be read considering its limitations and strengths. Due to privacy reasons, we were not able obtain the exact date of positivity and outcomes, thus we could only consider the week in which the event occurred. For the same reasons, we were not able to retrieve data on patients' comorbidities or health statuses, other than sex and age. Furthermore, the socio-economic features of the area were estimated based on the last available Italian deprivation index data which dates to 2011. Finally, the data focus on a relatively confined geographic area. Although this may appear to limit the generalizability of the findings, adapting models to encompass diverse and relevant exposures that impact COVID-19 related outcomes, enhances their applicability across various contexts, thereby enabling the adaptation of our findings to different regions. Another issue to consider is the evolution over time of the available therapeutic strategies and its potential impact on the risk of hospitalization and death, given that the clinical picture of COVID-19 was a novel situation, with its pathogenetic understanding having varied over time. In the very early stages, with the pathogenetic mechanism not yet clear, the therapy for severely ill patients primarily included the use of antibiotics, steroids, low molecular weight heparin, and ventilatory support. For patients with a less severe clinical situation, a watchful waiting strategy was employed, along with the use of paracetamol and symptomatic drugs for respiratory issues, gradually transitioning to the use of low molecular weight heparin in patients with a higher thromboembolic risk at home. Starting from May 2020, the use of oral corticosteroids was also implemented for non-hospitalized patients. Between late spring 2020 and autumn 2020, there was a discontinuation of the use of paracetamol, replaced using NSAIDs. However, only in the later stages, of the pandemic, starting from autumn 2021, therapeutic strategies based on more specific drugs such as monoclonal antibodies and antiviral drugs were implemented extensively, and this timeframe is not included in the period under study in our research. Finally, results for some climate and environmental factors were characterized by high variability and imprecision of the estimates, suggesting some caution in their interpretation.

This study has indeed numerous strengths as well. Firstly, our results are grounded in a large sample size (about 68500 who tested positive to a SARS-CoV-2 real-time polymerase chain reaction rhino-pharyngeal swab performed between February 21, 2020, and August 30, 2021), a valuable asset given the challenges associated with data collection during the early stages of the pandemic. Secondly, we investigated for the first time the individual-level risk of severe COVID-19 outcomes comprehensively and simultaneously across four exposure domains (environmental, climatic, socio-economic, and non-pharmacological interventions). Moreover, the presence of a free, public healthcare system in Italy implies minimal deficiencies depending on socio-economic status in testing and admissions. Finally, the consistency of our results both internal and with the existing literature underscores the reliability of the collected data and the validity of the employed methodologies.

5. Conclusions

In conclusion, the findings of this study hold significant implications from a public health perspective, offering valuable insights for policymakers in managing future pandemics. Firstly, our results may help guide the adaptation of local preventive healthcare policies by enabling targeted interventions and more efficient allocation of healthcare resources. Furthermore, understanding behavioral characteristics and health consequences related to geographic exposures (both environmental and climatic) and non-pharmacological interventions allows the development of personalized preventive interventions, fostering effective precision public health strategies. Our study also underscores the importance of recognizing socio-economic determinants in assessing the impact of pandemics, aiding in the identification of vulnerable groups, and reducing healthcare disparities and inequities. Moreover, the comprehension of risk factors associated with severe outcomes, such as hospitalization and mortality, is pivotal for planning responses to similar health emergencies in the future. The application and sharing of our model with communities grappling with COVID-19 challenges or pathogens with similar behavior could foster national and international collaboration in pandemic mitigation efforts and preparedness for future events. Ultimately, our findings may serve as a resource for guiding policy decisions, improving healthcare practices, and safeguarding public health in future pandemics, with significant benefits for the refinement and updating of pandemic response plans by healthcare authorities.

Competing interests

The authors have no relevant financial or non-financial interests to disclose that are relevant to the content of this article.

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Ethics approval

The study was approved by the Ethics Committee of the Area Vasta Emilia Nord (protocol no. AOU 0028505/21 approved on September 23, 2021) and was carried out in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

CRediT authorship contribution statement

Lucia Palandri: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cristiana Rizzi:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Vittoria Vandelli:** Writing – review & editing, Methodology, Data curation. **Tommaso Filippini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation. **Alessandro Ghinoi:** Writing – review & editing, Investigation, Data curation. **Giuliano Carrozzi:** Writing – review & editing, Investigation, Data curation. **Gianfranco De Girolamo:** Writing – review & editing, Investigation, Data curation. **Isabella Morlini:** Writing – review & editing, Supervision, Methodology. **Paola Coratza:** Writing – review & editing, Methodology, Data curation. **Enrico Giovannetti:** Writing – review & editing, Methodology, Data curation. **Margherita Russo:** Writing – review & editing, Supervision, Funding acquisition. **Mauro Soldati:** Writing – review & editing, Supervision, Funding acquisition. **Elena Righi:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **DISCOV-19 study group:** Data curation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2024.114471.

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