

1. Introduction

The first indigenous case of COVID-19 in Italy was diagnosed on February 20, 2020. Despite the isolation of potential hotspots in eleven affected municipalities ('red areas') and two national lockdowns established on February 23 and March 8–9, the outbreak quickly spread throughout Northern Italy and particularly in the Lombardy, Veneto and Emilia-Romagna regions (Gabutti et al., 2020; Ministry of Health, 2020). The later and more intensive lockdown, which started on March 8 in almost the entire territory of these three regions and on March 9 over all of Italy, was effective in slowing and curbing the infection, with a flattening and then a reversal of the outbreak beginning 9 days later. Further restrictions were established on March 22, including closure of all non-essential activities and prohibition of movements out of the municipality of residence.

Northern Italy is the most heavily industrialized and polluted area of Italy (EEA, 2019). The rapid and more intense spread of COVID-19 in Northern Italy, following the initial outbreak in densely populated and polluted Wuhan, China, prompted the hypothesis that the spread of the SARS-CoV-2 infection and possibly the severity of the associated COVID-19 disease was related to high air pollution levels (Coccia, 2020; Conticini et al., 2020; RIAS, 2020; SIMA, 2020; Watts and Kommenda, 2020).

Though there is some evidence that air pollution may enhance the susceptibility to viral infections including that by SARS-CoV-2 (Barcelo, 2020; Chen et al., 2010; Domingo and Rovira, 2020; Peng et al., 2020; Tsatsakis et al., 2020), the connection is still speculative. Transmission of airborne infections such as that due to SARS-CoV-2 occurs mainly through droplets and aerosols in the vicinity of infected individuals (Gabutti et al., 2020), but airborne particles might serve as carriers for pathogens (Setti et al., 2020a; SIMA, 2020; Zhao et al., 2019). Another possible mechanism linking air pollution to SARS-CoV-2 infection and COVID-19 might be higher susceptibility to respiratory viral diseases induced by air pollutants, through damage to respiratory tissue, immune dysregulation, over-expression of inflammatory cytokines and chemokines leading to innate immune system hyper-activation (Conticini et al., 2020) or ACE-2 receptor overexpression (Frontera et al., 2020).

Among the most commonly investigated air contaminants, nitrogen dioxide (NO₂) is a secondary pollutant formed by combustion processes, primarily from road transport (41%), energy production (22%), energy use from households and commercial activities (13%), and from industry (13%) (EEA, 2020). NO₂ is used for air pollution monitoring, with a threshold yearly average of 40 µg/m³ according to both European and WHO standards (EEA, 2019). In 2017 around 7% of the European urban population was exposed to concentrations above the annual EU limit (EEA, 2019). Traffic-related NO₂ exposure has been shown to be associated with increased risk of asthma and decreased lung function (Bowatte et al., 2017; Cai et al., 2017; McCreanor et al., 2007) and also rhinitis in adult population (Cesaroni et al., 2008; de Marco et al., 2002). In addition, high NO₂ levels has been associated with increased mortality for all causes, cardiovascular and respiratory mortality (Brunekreef et al., 2009; Eum et al., 2019; Hoek et al., 2013), and also pneumonia in older adults (Eum et al., 2019). With reference to SARS-CoV-2 infection, a recent spatial analysis has highlighted that up to 78% of COVID-19 deaths occurred in the five European areas located in Italy and Spain also showing the highest NO₂ levels, thus indicating a possible contribution to fatality by NO₂ long-term exposure (Ogen, 2020). In addition, a recent Chinese study showed a positive association between short-term exposure to air pollutants (i.e. particulate matter, sulfur dioxide, carbon monoxide, ozone and nitrogen dioxide) and newly diagnosed COVID-19 confirmed cases (Zhu et al., 2020), and other studies suggested a positive association with poor Air Quality Index (Li et al., 2020; Zoran et al., 2020).

The aim of our study was to investigate the relation between levels of air pollution in Northern Italy, assessed through remote-sensing satellite information on tropospheric NO₂, and subsequent spread of the

SARS-CoV-2 infection using publicly available data on newly-diagnosed infected cases.

2. Methods

2.1. Study area

We studied the Lombardy, Veneto and Emilia-Romagna regions of Northern Italy, which have a population of 19.4 million people, around 30% of Italian population, and accounted for 82% of Italian cases of SARS-CoV-2 infection on March 8, 2020 (Ministry of Health, 2020) with more severe forms of the disease requiring intensive care unit admission (Frontera et al., 2020). These regions contribute about 40% of the gross national product (ISTAT, 2020b), and are also characterized by the highest number of workers in the international export business sector (ISTAT, 2020a).

2.2. Health endpoints

The number of new daily SARS-CoV-2 positive cases was available by region and province of diagnosis from the national governmental website (CPD, 2020). From these data we computed prevalence rates, using population data for the study provinces from the Italian National Institute of Statistic website (ISTAT, 2020b).

2.3. Environmental exposure assessment

To assess the environmental pollution characterizing the study area before onset of the outbreak, we used daily information for the 1–23 February period from the Copernicus Open Access Hub-Sentinel-5P mission. Through this source, the European Space Agency (ESA) makes satellite data publicly available for the entire Europe (ESA, 2020). We focused on the geolocated (with a spatial resolution of 7 × 7 km²) tropospheric column of nitrogen dioxide reported by ESA Sentinel-5P, made available after Near Real Time (NRT) processing (typically 3 h from sensing), and, after addition, Offline (OFFL) processing (5 days after sensing time) (Eskes et al., 2019).

We collected all satellite images related to the area of interest (the provinces of the three study regions) for each day of the analysis period, and we computed population-weighted average of NO₂ values (in µmol/m²) for each province. Data about NO₂ were considered missing for one or more days when satellite coverage in those days decreased below 30% of the spatial units (provinces) for cloud-covered scenes or snow/ice on the surface influencing satellite image reliability (Eskes et al., 2019). We also validated satellite data through measured ground-level NO₂ concentration by monitoring stations, finding a high correlation between satellite and measured provincial average NO₂, with Pearson correlation coefficients ranging from 0.34 (Sondrio) to 0.81 (Cremona).

To control for population mobility, a possible confounding factor, we collected data on mobile phone daily movements through anonymous data of the SIM cards of residents (approximately 27 million people) processed and made available by Teralytics (Polzer, 2020). Information on the position of mobile telephones is available through the Call Detail Records (CDR), from which transport models can describe daily trip chains. We used daily movements in Italy available from February 1 through March 27 divided by the population in each province. We also retrieved temperature data publicly available from the European Centre for Medium-Range Weather Forecasts website (ECMWF, 2020), and relative humidity that has been calculated using environmental temperature and dewpoint temperature according previous method (Lawrence, 2005). We also considered as a potential confounder the presence of international airports in the study provinces for which the traffic flow was higher than 100,000 passengers in January 2020 (ASSAEROPORTI, 2020). This criterion included airports in Milan, Bergamo, Varese in Lombardy, Venice, Verona and Treviso in Veneto, and Bologna in Emilia-Romagna.

2.4. Data analysis

To assess the average amount of air pollution preceding the onset of the SARS-CoV-2 outbreak, we modeled the time-series of daily NO₂ tropospheric levels from February 1 to 24 using a linear regression taking into account heteroskedasticity and autocorrelation up to 7 days using a Newey–West estimator (Newey and West, 1987). We also modeled these values after the lockdowns. We then examined the relation between NO₂ levels before February 24, using the estimated NO₂ levels on February 12, which is the midpoint of the period before the lockdown, and SARS-CoV-2 infection prevalence rates at several time points: 14 days (corresponding to the period between outbreak onset and the establishment of the tight lockdown), 28 and 42 days, corresponding to March 8, March 22, and April 5. We used restricted cubic spline regression analysis fitting a model with three fixed knots (10th, 50th and 90th percentiles) according to Harrell's method (Harrell, 2001) to assess the shape of the relation.

We also collected information on other possible confounding factors, including population density and age distribution in 2019, percentage of population commuting daily for work or school, percentage of single-

member families, and percentage of dwellings with one resident only based on 2011 census data, the latest available at provincial level (ISTAT, 2020b).

We performed the analysis within a multivariable model adjusting for population density (number of inhabitants per km²), an index indicating age of the population (ratio between resident population aged ≥65 years and those aged ≤14 years), people mobility (measured using number of movements of mobile telephones before the lockdown), temperature (°C), relative humidity in the three subsequent periods (in percentage), and airport presence (yes/no). We alternatively further added to the model the percentage of population commuting daily outside the municipality of residence for work or study, single member families, or dwellings occupied by only one resident.

3. Results

Fig. 1 shows the average tropospheric levels of NO₂ in study provinces before the disease outbreak, and in the subsequent periods during the spread of SARS-CoV-2 infection, when NO₂ levels steadily decreased. In particular, before the outbreak the

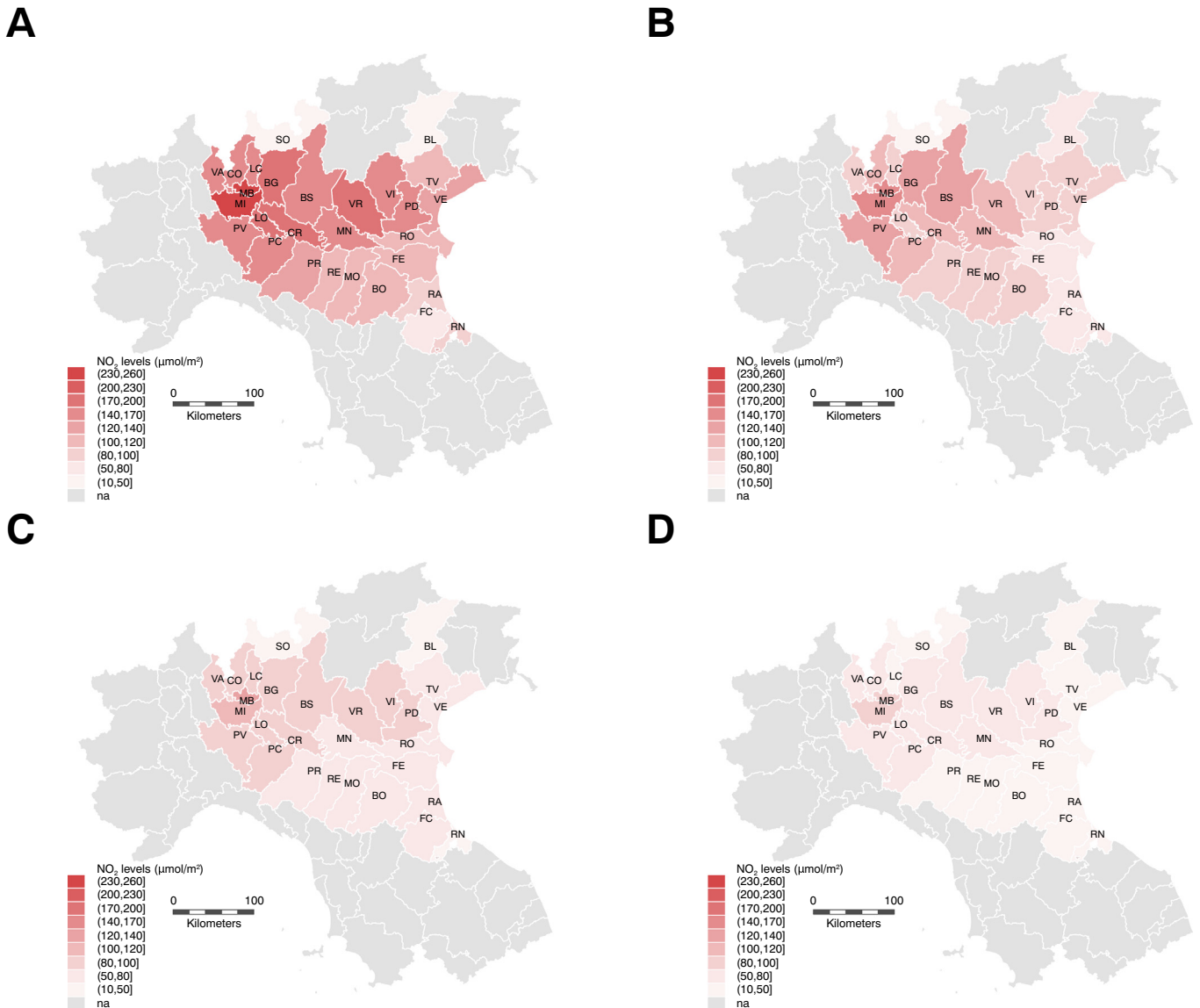


Fig. 1. Northern Italy study area showing levels of NO₂ tropospheric levels (µmol/m³) before the first lockdown (A), and in the subsequent periods February 24–March 8 (B), March 8–March 22 (C), and after March 22 (D).

average NO₂ levels were high in Lombardy (193 µmol/m²), Milan (238 µmol/m²) and Monza/Brianza (243 µmol/m²), and they fell below 100 µmol/m² in all investigated provinces in the period following the tightest mobility restrictions.

Table 1 reports the province-specific prevalence rates of the SARS-CoV-2 infection in the three follow-up time points considered in the study, i.e. the one corresponding to the institution of the tight lockdown (March 8), and the next two 2-week periods, along with corresponding NO₂ pollution levels before and after the detection of the outbreak (February 24).

We first fit a spline curve to the crude data. There was an increase in prevalence rates can be noted at low levels of NO₂, with a plateau above 150 µmol/m² (Fig. S1). In multivariable analysis adjusting for population density, elderly population, airport presence, people mobility before February 24, and temperature and relative humidity in the two weeks before prevalence assessment (Fig. 2), NO₂ levels in the pre-outbreak period were not meaningfully associated with COVID-19 prevalence rates at any of the three follow-up time points, up to approximately 130 µmol/m² of NO₂ levels. Above 130 µmol/m² of NO₂ levels, however, there was a higher prevalence of COVID-19 with increasing levels of air pollution, with a similar curve relating air pollution to prevalence for each of the three time periods. Further addition of possible confounding factors, such as percentage of daily commuters outside the municipality of residence (Fig. S2), percentage of single-member families (Fig. S3), and percentage of dwellings occupied by only one resident (Fig. S4), did not appreciably change the results. In these analyses, the limited precision inherent in these ecological data are reflected in the broad confidence bands.

4. Discussion

In this study, we found a positive association between levels of NO₂ levels and subsequent prevalence of SARS-CoV-2 positivity in Northern Italy, though this occurred only at high levels of NO₂. This relation is consistent with severe outdoor air pollution enhancing the spread of the SARS-CoV-2 virus, possibly by altering the immunological status and thus increasing individual susceptibility to infectious diseases (Ibironke et al., 2019; Marchini et al., 2020; Rivas-Santiago et al., 2015; Williams et al., 2011). The area of the study comprises the densest industrial, trading and agricultural zone in Italy, with an orography that favors the stagnation of pollutants. This region has seen some of the worst air pollution in Europe (EEA, 2019; Mazzola et al., 2010). Within this area, high levels of air pollution have been associated with increased mortality and hospitalization for both cardiovascular and respiratory diseases (Carugno et al., 2016; Fattore et al., 2011).

A positive association between spread of the SARS-CoV-2 outbreak in Italy and excesses of particulate matter at monitoring stations has also been reported (CPD, 2020; Setti et al., 2020b), and in the US an increase of 1 µg/m³ in particular matter (PM_{2.5}) has been associated with a 15% increase in mortality from COVID-19 (Wu et al., 2020). High air pollution levels could also have favored the spread of another coronavirus-induced disease, SARS, based on the positive correlation between air pollution and its lethality in Chinese provinces (Cui et al., 2003). In addition, a study carried out in Milan metropolitan area (Lombardy region) found a positive association between COVID-19 new daily cases and particulate matter levels, with Pearson correlation coefficient between average and maximum PM₁₀ levels and daily new cases of 0.35 and 0.51, respectively (Zoran et al., 2020). We used tropospheric NO₂

Table 1
Number of total SARS-CoV-2 positive cases and prevalence rate on March 8, March 22, and April 5 and predicted NO₂ tropospheric levels (µmol/m²) before the lockdown, in the subsequent periods after partial lockdown (February 24–March 8), after full lockdown (March 8–March 22), and after March 22.

	Population at Jan 1, 2019 ^a	Total cases			Prevalence rate (per 100,000)			NO ₂ levels (µmol/m ²)			
		Mar 8	Mar 22	Apr 5	Mar 8	Mar 22	Apr 5	Before Feb 24	After Feb 24		
									Feb 24–Mar 8	Mar 8–Mar 22	After Mar 22
Lombardy	10,060,574	4189	27,206	50,455	41.6	270.4	501.5	198	126	98	72
Bergamo (BG)	1,114,590	997	6296	9712	89.5	557.7	871.4	199	124	93	59
Brescia (BS)	1,265,954	501	5317	9340	39.6	420.0	737.8	169	120	91	61
Como (CO)	599,204	27	512	1384	4.5	85.4	231	163	101	95	64
Cremona (CR)	358,955	665	2895	4233	185.3	806.5	1179.3	177	107	84	60
Lecco (LC)	337,380	53	872	1678	15.7	258.5	497.4	151	92	81	48
Lodi (LO)	230,198	853	1772	2255	370.6	769.8	979.6	173	98	83	74
Mantua (MN)	412,292	56	905	3046	13.6	219.5	348.5	159	105	74	53
Milan (MI)	3,250,315	406	5096	11,230	12.5	156.9	345.5	245	157	111	98
Monza/Brianza (MB)	873,935	59	1108	3046	6.8	126.8	348.5	255	153	138	80
Pavia (PV)	545,888	243	1306	2619	44.5	239.2	479.8	147	98	72	50
Sondrio (SO)	181,095	6	205	591	3.3	113.2	326.3	33	25	22	29
Varese (VA)	890,768	32	386	1191	3.6	43.3	133.7	166	99	92	60
Veneto	4,905,854	670	5122	11,226	13.7	104.4	228.8	136	94	75	50
Belluno (BL)	202,950	23	226	538	11.3	111.4	265.1	50	56	31	29
Padua (PD)	937,908	255	1277	2744	27.2	136.2	292.6	147	88	84	55
Rovigo (RO)	234,937	5	76	186	2.1	32.3	79.2	118	68	56	42
Treviso (TV)	887,806	126	935	1712	14.2	105.3	192.8	108	96	59	42
Venezia (VE)	853,338	126	732	1425	14.8	85.8	167	126	94	66	46
Verona (VR)	926,497	63	1046	2688	6.8	112.9	290.1	181	114	97	59
Vicenza (VI)	862,418	50	631	1647	5.8	73.2	191	141	97	84	54
Emilia-Romagna	4,459,477	1180	7555	17,089	26.5	168.4	383.2	109	81	66	38
Bologna (BO)	1,014,619	62	674	2521	6.1	66.4	248.5	109	86	71	37
Ferrara (FE)	345,691	6	150	488	1.7	43.4	141.2	104	71	55	39
Forlì-Cesena (FC)	394,627	15	329	977	3.8	83.4	247.6	80	61	51	29
Modena (MO)	705,393	97	1010	2609	13.8	143.2	369.9	117	95	70	42
Parma (PR)	451,631	276	1209	2275	61.1	267.7	503.7	121	87	72	42
Piacenza (PC)	287,152	528	1765	2892	183.9	614.7	1007.1	140	113	90	58
Ravenna (RA)	389,456	13	309	708	3.3	79.3	181.8	95	67	60	31
Reggio Emilia (RE)	531,891	70	1167	3066	13.2	219.4	576.4	118	83	68	43
Rimini (RN)	339,017	113	942	1553	33.3	277.9	458.1	90	53	40	23
Italy	60,359,546	7375	59,138	128,948	12.2	98.0	213.6				

^a Most recent data available from Italian National Institute of Statistic (ISTAT, 2020b).

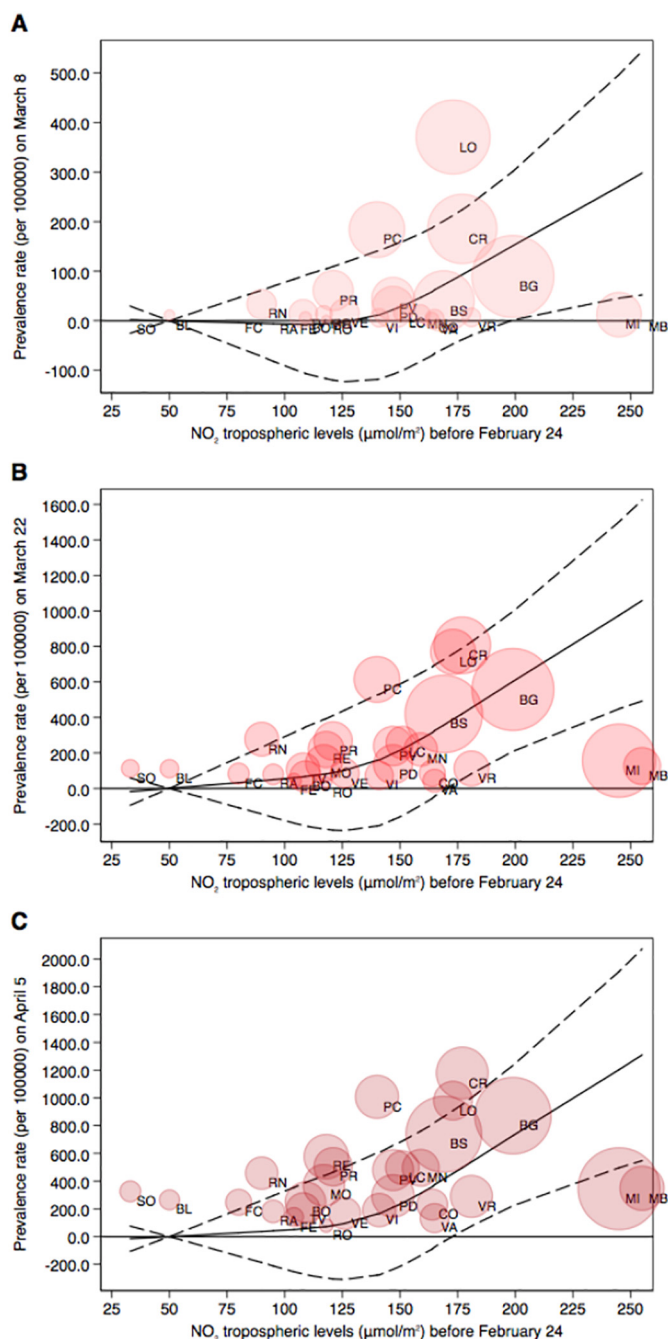


Fig. 2. Restricted cubic spline regression analysis between NO_2 tropospheric levels ($\mu\text{mol}/\text{m}^2$) before the spread of the outbreak and SARS-CoV-2 positivity prevalence (cases per 100,000) in the three periods after the lockdown dates (A: February 24–March 8; B: March 8–March 22; C: March 22–April 5). Results presented SARS-CoV-2 infection prevalence rate (solid line) with 95% confidence interval (dash lines) in a multivariable model adjusted for population density, an index indicating age of the population, people mobility measured from telephone movements before the lockdown, temperature ($^{\circ}\text{C}$) and relative humidity in the three subsequent periods, and airport presence. Shaded circles are weighted on number of cases corresponding to the prevalence rates at each time point.

levels as a proxy for overall air pollution. This metric was closely associated with ground levels of this contaminant in a validation study in the study area as well as in other European urban areas (Ialongo et al., 2020; Lorente et al., 2019).

In vitro studies have shown that NO_2 can alter expression and synthesis of pro-inflammatory mediators in human bronchial cells (Bayram et al., 2001; Blomberg et al., 1997; Blomberg et al., 1999;

Devalia et al., 1993; Mirowsky et al., 2016), thus increasing inflammation and hyperresponsiveness of epithelial cells. Also, both direct cytotoxicity and cytokine-mediated has been reported after NO_2 exposure of epithelial cells in the lung (Ayyagari et al., 2004; Persinger et al., 2002). Overall, these observations provide some biological plausibility for the association we and other detected. In addition, NO_2 levels are likely to mirror the air levels of other contaminants, such as particulate matter (Bigi et al., 2012), which also has deleterious effects on the immunity (Blomberg, 2000; Glencross et al., 2020).

Despite biologic plausibility, this study has important limitations. Most important is the potential for ecologic bias, because we used aggregated data. With aggregated data we could not take into account individual risk factors that affected the spread of infection, nor control directly for confounding at the individual level. Factors such as working in health care delivery, travel to China or other infected countries, residence in nursing homes, and individual contact with infected relatives, friends, or workmates were not controlled and differences in the distributions of these factors may have influenced the results. A further limitation was the inability to examine other clinical endpoints of COVID-19, but information on hospitalizations, deaths, and other outcomes were not publicly available at the provincial level. Finally, the effect estimates we computed were imprecise, as reflected in broad confidence intervals. Although these limitations preclude strong inferences from these ecologic data, our findings appear to confirm an association between heavy air pollution and spread of the SARS-CoV-2 virus.

Abbreviations

CDR	Call Detail Records
ESA	European Space Agency
NO_2	nitrogen dioxide
NRT	Near Real Time processing
OFFL	Offline processing
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2

CRedit authorship contribution statement

Tommaso Filippini: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Kenneth J. Rothman:** Formal analysis, Investigation, Writing - review & editing. **Alessia Goffi:** Data curation, Resources, Writing - review & editing. **Fabrizio Ferrari:** Data curation, Resources, Writing - review & editing. **Giuseppe Maffei:** Data curation, Methodology, Resources, Writing - review & editing. **Nicola Orsini:** Formal analysis, Methodology, Writing - review & editing. **Marco Vinceti:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Supported by grant 'UNIMORE FAR 2019 Interdisciplinare Linea FCRMO - Fondazione Cassa di Risparmio di Modena'.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2020.140278>.

References

- ASSAEROPORTI, 2020. January 2020 Statistics. Associazione Italiana Gestori di Aeroporti http://assaerporti.com/statistiche_202001/, Accessed date: 12 June 2020.
- Ayyagari, V.N., Januszkiewicz, A., Nath, J., 2004. Pro-inflammatory responses of human bronchial epithelial cells to acute nitrogen dioxide exposure. *Toxicology* 197, 149–164. <https://doi.org/10.1016/j.tox.2003.12.017>.
- Barcelo, D., 2020. An environmental and health perspective for COVID-19 outbreak: Meteorology and air quality influence, sewage epidemiology indicator, hospitals disinfection, drug therapies and recommendations. *J. Environ. Chem. Eng.* 8, 104006. <https://doi.org/10.1016/j.jece.2020.104006>.
- Bayram, H., Sapsford, R.J., Abdelaziz, M.M., Khair, O.A., 2001. Effect of ozone and nitrogen dioxide on the release of proinflammatory mediators from bronchial epithelial cells of nonatopic nonasthmatic subjects and atopic asthmatic patients in vitro. *J. Allergy Clin. Immunol.* 107, 287–294. <https://doi.org/10.1067/mai.2001.111141>.
- Bigi, A., Ghermandi, G., Harrison, R.M., 2012. Analysis of the air pollution climate at a background site in the Po valley. *J. Environ. Monit.* 14, 552–563. <https://doi.org/10.1039/c1em10728c>.
- Blomberg, A., 2000. Airway inflammatory and antioxidant responses to oxidative and particulate air pollutants - experimental exposure studies in humans. *Clin. Exp. Allergy* 30, 310–317. <https://doi.org/10.1046/j.1365-2222.2000.00814.x>.
- Blomberg, A., Krishna, M.T., Bocchino, V., Biscione, G.L., Shute, J.K., Kelly, F.J., et al., 1997. The inflammatory effects of 2 ppm NO₂ on the airways of healthy subjects. *Am. J. Respir. Crit. Care Med.* 156, 418–424. <https://doi.org/10.1164/ajrccm.156.2.9612042>.
- Blomberg, A., Krishna, M.T., Helleday, R., Soderberg, M., Ledin, M.C., Kelly, F.J., et al., 1999. Persistent airway inflammation but accommodated antioxidant and lung function responses after repeated daily exposure to nitrogen dioxide. *Am. J. Respir. Crit. Care Med.* 159, 536–543. <https://doi.org/10.1164/ajrccm.159.2.9711068>.
- Bowatte, G., Erbas, B., Lodge, C.J., Knibbs, L.D., Gurrin, L.C., Marks, G.B., et al., 2017. Traffic-related air pollution exposure over a 5-year period is associated with increased risk of asthma and poor lung function in middle age. *Eur. Respir. J.* 50, 1602357. <https://doi.org/10.1183/13993003.02357-2016>.
- Brunekreef, B., Beelen, R., Hoek, G., Schouten, L., Bausch-Goldbohm, S., Fischer, P., et al., 2009. Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: the NLCS-AIR study. *Res. Rep. Health Eff. Inst.* 5–71 (discussion 73–89).
- Cai, Y., Zijlema, W.L., Doiron, D., Blangiardo, M., Burton, P.R., Fortier, I., et al., 2017. Ambient air pollution, traffic noise and adult asthma prevalence: a BioSHaRE approach. *Eur. Respir. J.* 49. <https://doi.org/10.1183/13993003.02127-2015>.
- Carugno, M., Consonni, D., Randi, G., Catelan, D., Grisotto, L., Bertazzi, P.A., et al., 2016. Air pollution exposure, cause-specific deaths and hospitalizations in a highly polluted Italian region. *Environ. Res.* 147, 415–424. <https://doi.org/10.1016/j.envres.2016.03.003>.
- Cesaroni, G., Badaloni, C., Porta, D., Forastiere, F., Perucci, C.A., 2008. Comparison between various indices of exposure to traffic-related air pollution and their impact on respiratory health in adults. *Occup. Environ. Med.* 65, 683–690. <https://doi.org/10.1136/oem.2007.037846>.
- Chen, P.S., Tsai, F.T., Lin, C.K., Yang, C.Y., Chan, C.C., Young, C.Y., et al., 2010. Ambient influenza and avian influenza virus during dust storm days and background days. *Environ. Health Perspect.* 118, 1211–1216. <https://doi.org/10.1289/ehp.0901782>.
- Coccia, M., 2020. Factors determining the diffusion of COVID-19 and suggested strategy to prevent future accelerated viral infectivity similar to COVID. *Sci. Total Environ.* 729, 138474. <https://doi.org/10.1016/j.scitotenv.2020.138474>.
- Conticini, E., Frediani, B., Caro, D., 2020. Can atmospheric pollution be considered a cofactor in extremely high level of SARS-CoV-2 lethality in Northern Italy? *Environ. Pollut.* 261, 114465. <https://doi.org/10.1016/j.envpol.2020.114465>.
- CPD, 2020. Italian civil protection department: COVID-19 data. <https://github.com/pcm-dpc/COVID-19>, Accessed date: 12 June 2020.
- Cui, Y., Zhang, Z.F., Froines, J., Zhao, J., Wang, H., Yu, S.Z., et al., 2003. Air pollution and case fatality of SARS in the People's Republic of China: An ecologic study. *Environ. Health* 2, 15. <https://doi.org/10.1186/1476-069X-2-15>.
- de Marco, R., Poli, A., Ferrari, M., Accordini, S., Giammanco, G., Bugiani, M., et al., 2002. The impact of climate and traffic-related NO₂ on the prevalence of asthma and allergic rhinitis in Italy. *Clin. Exp. Allergy* 32, 1405–1412. <https://doi.org/10.1046/j.1365-2745.2002.01466.x>.
- Devalia, J.L., Campbell, A.M., Sapsford, R.J., Rusznak, C., Quint, D., Godard, P., et al., 1993. Effect of nitrogen dioxide on synthesis of inflammatory cytokines expressed by human bronchial epithelial cells in vitro. *Am. J. Respir. Cell Mol. Biol.* 9, 271–278. <https://doi.org/10.1165/ajrcmb.9.3.271>.
- Domingo, J.L., Rovira, J., 2020. Effects of air pollutants on the transmission and severity of respiratory viral infections. *Environ. Res.* 187, 109650. <https://doi.org/10.1016/j.envres.2020.109650>.
- ECMWF, 2020. ERA5 dataset European Centre for Medium-Range Weather Forecasts. <https://www.ecmwf.int/en/forecasts/datasets/reanalysis-datasets/era5>, Accessed date: 6 December 2020.
- EEA, 2019. In: European Environment Agency (Ed.), EEA Report No 10/2019 - Air Quality in Europe 2019 Copenhagen, Denmark. <https://www.eea.europa.eu/publications/air-quality-in-europe-2019>, Accessed date: 12 June 2020.
- EEA, 2020. In: European Environment Agency (Ed.), The European Environment State and Outlook 2020. EEA, Luxembourg <https://www.eea.europa.eu/publications/soer-2020>, Accessed date: 12 June 2020.
- ESA, 2020. Sentinel-5P Data. European Space Agency https://www.esa.int/Applications/Observing_the_Earth/Copernicus/Sentinel-5P, Accessed date: 12 June 2020.
- Eskes, H., van Geffen, J., Boersma, F., Eichmann, K.-U., Apituley, A., Pedergnana, M., et al., 2019. In: Royal Netherlands Meteorological Institute (Ed.), Sentinel-5 Precursor/TROPOMI Level 2 Product User Manual Nitrogen dioxide. Royal Netherlands Meteorological Institute <https://sentinel.esa.int/documents/247904/2474726/Sentinel-5P-Level-2-Product-User-Manual-Nitrogen-Dioxide>, Accessed date: 12 June 2020.
- Eum, K.D., Kazemiparkouhi, F., Wang, B., Manjourides, J., Pun, V., Pavlu, V., et al., 2019. Long-term NO₂ exposures and cause-specific mortality in American older adults. *Environ. Int.* 124, 10–15. <https://doi.org/10.1016/j.envint.2018.12.060>.
- Fattore, E., Paiano, V., Borgini, A., Tittarelli, A., Bertoldi, M., Crosignani, P., et al., 2011. Human health risk in relation to air quality in two municipalities in an industrialized area of Northern Italy. *Environ. Res.* 111, 1321–1327. <https://doi.org/10.1016/j.envres.2011.06.012>.
- Frontera, A., Cianfanelli, L., Vlachos, K., Landoni, G., Cremona, G., 2020. Severe air pollution links to higher mortality in COVID-19 patients: The “double-hit” hypothesis. *J. Inf. Secur.* <https://doi.org/10.1016/j.jinf.2020.05.031>.
- Gabutti, G., d'Anchera, E., Sandri, F., Savio, M., Stefanati, A., 2020. Coronavirus: update related to the current outbreak of COVID-19. *Infect. Dis. Ther.* 9, 241–253. <https://doi.org/10.1007/s40121-020-00295-5>.
- Glencross, D.A., Ho, T.R., Camina, N., Hawrylowicz, C.M., Pfeffer, P.E., 2020. Air pollution and its effects on the immune system. *Free Radic. Biol. Med.* 151, 56–68. <https://doi.org/10.1016/j.freeradbiomed.2020.01.179>.
- Harrell, F.E., 2001. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. Springer-Verlag, New York.
- Hoek, G., Krishnan, R.M., Beelen, R., Peters, A., Ostro, B., Brunekreef, B., et al., 2013. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ. Health* 12, 43. <https://doi.org/10.1186/1476-069X-12-43>.
- Ialongo, I., Virta, H., Eskes, H., Hovila, J., Douros, J., 2020. Comparison of TROPOMI/Sentinel-5 Precursor NO₂ observations with ground-based measurements in Helsinki. *Atmos. Meas. Tech.* 13, 205–218. <https://doi.org/10.5194/amt-13-205-2020>.
- Ibironke, O., Carranza, C., Sarkar, S., Torres, M., Choi, H.T., Nwoko, J., et al., 2019. Urban air pollution particulates suppress human T-cell responses to mycobacterium tuberculosis. *Int. J. Environ. Res. Public Health* 16, 4112. <https://doi.org/10.3390/ijerph16214112>.
- ISTAT, 2020a. Coeweb - Statistiche del commercio estero. Italian National Institute of Statistics <https://www.coeweb.istat.it>, Accessed date: 12 June 2020.
- ISTAT, 2020b. Data from the Italian National Institute of Statistics. <https://www.istat.it/it/popolazione-e-famiglie>, Accessed date: 6 December 2020.
- Lawrence, M.G., 2005. The relationship between relative humidity and the dewpoint temperature in moist air: a simple conversion and applications. *Bull. Am. Meteorol. Soc.* 86, 225–234. <https://doi.org/10.1175/BAMS-86-2-225>.
- Li, H., Xu, X.L., Dai, D.W., Huang, Z.Y., Ma, Z., Guan, Y.J., 2020. Air pollution and temperature are associated with increased COVID-19 incidence: a time series study. *Int. J. Infect. Dis.* <https://doi.org/10.1016/j.ijid.2020.05.076>.
- Lorente, A., Boersma, K.F., Eskes, H.J., Veefkind, J.P., van Geffen, J., de Zeeuw, M.B., et al., 2019. Quantification of nitrogen oxides emissions from build-up of pollution over Paris with TROPOMI. *Sci. Rep.* 9, 20033. <https://doi.org/10.1038/s41598-019-56428-5>.
- Marchini, T., Zirlik, A., Wolf, D., 2020. Pathogenic role of air pollution particulate matter in cardiometabolic disease: Evidence from mice and humans. *Antioxid. Redox Signal.* <https://doi.org/10.1089/ars.2020.8096>.
- Mazzola, M., Lanconelli, C., Lupi, A., Busetto, M., Vitale, V., Tomasi, C., 2010. Columnar aerosol optical properties in the Po Valley, Italy, from MFRSR data. *J. Geophys. Res.* Atmos. 115, D17206. <https://doi.org/10.1029/2009JD013310>.
- McCreanor, J., Cullinan, P., Nieuwenhuijsen, M.J., Stewart-Evans, J., Malliarou, E., Jarup, L., et al., 2007. Respiratory effects of exposure to diesel traffic in persons with asthma. *N. Engl. J. Med.* 357, 2348–2358. <https://doi.org/10.1056/NEJMoa071535>.
- Ministry of Health, 2020. Official Italian statistics on SARS-CoV-2, March 8, 2020. http://www.salute.gov.it/imgs/C_17_pagineArea_5351_0_file.pdf, Accessed date: 6 December 2020.
- Mirowsky, J.E., Dailey, L.A., Devlin, R.B., 2016. Differential expression of pro-inflammatory and oxidative stress mediators induced by nitrogen dioxide and ozone in primary human bronchial epithelial cells. *Inhal. Toxicol.* 28, 374–382. <https://doi.org/10.1080/08958378.2016.1185199>.
- Newey, W.K., West, K.D., 1987. A simple, positive semi-definite, heteroskedasticity and autocorrelation consistent covariance matrix. *Econometrica* 55, 703–708. <https://doi.org/10.2307/1913610>.
- Ogen, Y., 2020. Assessing nitrogen dioxide (NO₂) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci. Total Environ.* 726, 138605. <https://doi.org/10.1016/j.scitotenv.2020.138605>.
- Peng, L., Zhao, X., Tao, Y., Mi, S., Huang, J., Zhang, Q., 2020. The effects of air pollution and meteorological factors on measles cases in Lanzhou, China. *Environ. Sci. Pollut. Res. Int.* 27, 13524–13533. <https://doi.org/10.1007/s11356-020-07903-4>.
- Persinger, R.L., Poynter, M.E., Ckless, K., Janssen-Heininger, Y.M., 2002. Molecular mechanisms of nitrogen dioxide induced epithelial injury in the lung. *Mol. Cell. Biochem.* 234–235, 71–80. <https://doi.org/10.1023/A:1015973530559>.
- Polzer, G., 2020. La mappa della nostra era glaciale: così il coronavirus ha congelato l'Italia. La Repubblica, Italy <https://lab.gedidigital.it/repubblica/2020/cronaca/coronavirus-mappa-italia-impatto-sulla-mobilita/?ref=RHPPLF-BH-I252606083-C8-P3-S1.8-T1>, Accessed date: 12 June 2020.
- RIAS, 2020. Inquinamento atmosferico e COVID-19, Rete Italiana Ambiente e Salute. SCIRE <https://www.scienzainrete.it/articolo/inquinamento-atmosferico-e-covid-19/rete-italiana-ambiente-e-salute/2020-04-13>, Accessed date: 12 June 2020.
- Rivas-Santiago, C.E., Sarkar, S., Cantarella, P., Osornio-Vargas, A., Quintana-Belmares, R., Meng, Q., et al., 2015. Air pollution particulate matter alters antimicrobial respiratory epithelium innate immunity. *Infect. Immun.* 83, 2507–2517. <https://doi.org/10.1128/IAI.03018-14>.
- Setti, L., Passarini, F., De Gennaro, G., Barbieri, P., Perrone, M.G., Borelli, M., et al., 2020a. SARS-Cov-2RNA found on particulate matter of Bergamo in Northern Italy: first evidence. *Environ. Res.* 188, 109754. <https://doi.org/10.1016/j.envres.2020.109754>.

- Setti, L., Passarini, F., De Gennaro, G., Barbieri, P., Perrone, M.G., Piazzalunga, A., et al., 2020b. The potential role of particulate matter in the spreading of COVID-19 in northern Italy: first evidence-based research hypotheses. medRxiv <https://doi.org/10.1101/2020.04.11.20061713> 2020.04.11.20061713.
- SIMA, 2020. Position paper particulate matter and COVID-19 Italian Society of Environmental Medicine (SIMA). http://www.simaonline.it/wpsima/wp-content/uploads/2020/03/COVID_19_position-paper_ENG.pdf, Accessed date: 12 June 2020.
- Tsatsakis, A., Petrakis, D., Nikolouzakis, T.K., Docea, A.O., Calina, D., Vinceti, M., et al., 2020. COVID-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence. Food Chem. Toxicol. 141, 111418. <https://doi.org/10.1016/j.fct.2020.111418>.
- Watts, J., Kommenda, N., 2020. Coronavirus pandemic leading to huge drop in air pollution. The Guardian https://www.theguardian.com/environment/2020/mar/23/coronavirus-pandemic-leading-to-huge-drop-in-air-pollution?CMP=Share_iOSApp_Other, Accessed date: 26 April 2020.
- Williams, L., Ulrich, C.M., Larson, T., Wener, M.H., Wood, B., Chen-Levy, Z., et al., 2011. Fine particulate matter (PM_{2.5}) air pollution and immune status among women in the Seattle area. Arch. Environ. Occup. Health 66, 155–165. <https://doi.org/10.1080/19338244.2010.539636>.
- Wu, X., Nethery, R.C., Sabath, B.M., Braun, D., Dominici, F., 2020. Exposure to air pollution and COVID-19 mortality in the United States. medRxiv <https://doi.org/10.1101/2020.04.05.20054502> 2020.04.05.20054502.
- Zhao, Y., Richardson, B., Takle, E., Chai, L., Schmitt, D., Xin, H., 2019. Airborne transmission may have played a role in the spread of 2015 highly pathogenic avian influenza outbreaks in the United States. Sci. Rep. 9, 11755. <https://doi.org/10.1038/s41598-019-47788-z>.
- Zhu, Y., Xie, J., Huang, F., Cao, L., 2020. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. Sci. Total Environ. 727, 138704. <https://doi.org/10.1016/j.scitotenv.2020.138704>.
- Zoran, M.A., Savastru, R.S., Savastru, D.M., Tautan, M.N., 2020. Assessing the relationship between surface levels of PM_{2.5} and PM₁₀ particulate matter impact on COVID-19 in Milan, Italy. Sci. Total Environ. 738, 139825. <https://doi.org/10.1016/j.scitotenv.2020.139825>.