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Distance from the outbreak of infection, ozone pollution and public health consequences of SARS-CoV-2 epidemic: the HOPE method

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Background: Italy was the second country in the world, after China, to be hit by SARS-CoV-2 pandemic. Italy's experience teaches that steps to limit people's movement by imposing 'red zones' need to be put in place early by carefully identifying the cities to be included within these areas of quarantine. The assessment of the relationship between the distance from an established outbreak of SARS-CoV-2 infection with transmission-linked cases and mortality observed in other sites could provide useful information to identify the optimal radius of red zones. **Methods:** We investigated the relationship between SARS-CoV-2 cases and the distance of each Italian province from the first outbreak of SARS-CoV-2 epidemic in Italy (the city of Lodi placed in the Lombardia region). In 38 provinces of Lombardia and neighboring regions, we performed a breakpoint analysis to identify the radius of the red zone around Lodi minimizing epidemic spread and mortality in neighboring cities. **Results:** In all Italian provinces, a non-linear relationship was found between SARS-CoV-2 cases and distance from Lodi. In an analysis including the provinces of Lombardia and neighboring regions, SARS-CoV-2 cases and mortality increased when the distance from Lodi reduced below 92 and 140 km, respectively, and such relationships were amplified by ozone (O_3) pollution. **Conclusions:** The breakpoint analysis identifies the radius around the outbreak of Lodi minimizing the public health consequences of SARS-CoV-2 in neighboring cities. Such an approach can be useful to identify the red zones in future epidemics due to highly infective pathogens similar to SARS-CoV-2.

Introduction

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified worldwide in Wuhan, China, in December 2019.[1] In Europe, the first two imported cases of SARS-CoV-2 were found in Rome in January 2020 when two Chinese tourists were diagnosed to be affected by the virus whereas the first autochthonous case in Italy was a 38 year old man tested positive after returning back from Wuhan and identified in the province of Lodi (Codogno) in February 2020.[2] Thus, the province of Lodi (placed in the Lombardia Region) is considered the original outbreak of infection in Italy.[2] In February 2020, 11 northern Italian cities, having in common a high social interactivity due to their industrialization and business activities, were identified as clusters of infection and placed under quarantine. By the beginning of March 2020, the virus had spread to all Italian territories resulting consistently worse, in term of severity and incidence, in Northern compared to Southern Italy.[2] On 8 March 2020, the Italian Government expanded the quarantine to the Lombardia region and other 14 northern provinces. On 11 March 2020, the Italian Government prohibited nearly all commercial activities except for supermarkets and pharmacies and on 22 March 2020, a new decree closed all non-essential commercial activities and industries restricting people movement by imposing a national lockdown.

Social distancing, together with the use of wearing masks and washing hands, is considered one the most effective practices against SARS-CoV-2 pandemic. Indeed, the distance between related infection cases is a peculiar property of communicable disease dispersal although the distance between a single case and their infector is rarely assessable. Moving from individuals to populations, the analysis of the relationship between the distance from an established outbreak of infection in a specific region within a country with transmission-linked cases and excess mortality rate observed in other sites could provide useful information to assess the optimal radius of red zone around an outbreak of infection to be used in future epidemics of the same type (i.e. with similar R_0).

In this paper, we tested the following hypotheses: (i) Is there a relationship between the distance from Lodi (the original outbreak of COVID-19 infection in Italy) of each Italian province and the total SARS-CoV-2 cases in the same cities ($n = 107$) on 21 March 2020 (the day before the publication of the decree which extended further restrictions at national level)? (ii) In the area around the outbreak of infection (i.e. the area including the provinces of Lombardia and neighboring regions, $n = 38$ cities), is it possible to identify the optimal radius of the quarantine zone (i.e. the optimal distance from Lodi) which minimizes the spread of epidemic and excess mortality in neighboring cities? (iii) Does the ozone (O_3) pollution modify the relationship between the distance from Lodi and the public health consequences of COVID-19 epidemic observed in the provinces of Lombardia and neighboring regions? (iv) Given the fact that on 21 March 2020, the Veneto Region performed a higher number of swabs as compared to those made in Lombardia, Emilia Romagna, Piemonte and Trentino Alto Adige, does this strategy translate into a lower number of SARS-CoV-2

cases and lower excess mortality in the provinces of Veneto when matched to the provinces of the other four regions according to the distance from Lodi?

Methods

The Italian surveillance network monitors the COVID-19 epidemic through two daily data streams: (i) the flow of aggregate data sent by the Regions coordinated by the Ministry of Health, with the support of the Civil Protection and the National Institute of Health, to collect timely information on the total number of positive tests, deaths, hospitalizations and intensive care admissions in each Province of Italy; (ii) the flow of individual data sent by the Regions to the National Institute of Health (Covid-19 integrated surveillance, ordinance n.640 of the Civil Protection of 27/2/2020), which also includes demographic data, comorbidities, clinical status and its evolution over time, for a more accurate analysis. For the purpose of this paper, the total SARS-CoV-2 cases (including active cases, recovered/discharge patients and deceased) on 21 March 2020 in Italian provinces ($n = 107$) were obtained via a public data repository of Padua University, Department of Public Health,[3] which acquires the daily information from the National Civil Protection Department. We restricted the observation to 21 March 2020 to avoid the effect of the further limitations of the national lockdown (imposed by the Italian Government with the decree published on 22 March) on the link between the distance from Lodi, total SARS-CoV-2 cases and excess mortality. The percent increase in all-cause mortality in 38 provinces of Lombardia and neighboring regions (Piemonte, Emilia Romagna, Trentino Aldo Adige and Veneto) between the first trimester (January–March) 2020 and the average mortality rate of the same period between 2015 and 2019 was obtained via the survival tables of the Italian Institute of Statistics (ISTAT).[4] On 21 March 2020, the number of swabs per 10^4 inhabitants in Lombardia, Emilia Romagna, Piemonte, Trentino Aldo Adige and Veneto were extracted from the web site of Padua University, Department of Public Health[3] and normalized by the total number of residents in each region.[5] The effect modification by O_3 pollution on the relationship between the distance from Lodi, SARS-CoV-2 cases and excess mortality in 38 Italian provinces of the same regions was investigated by dividing the study sample into two groups according to the median value of days with $O_3 > 120\ \mu g/m^3$ (the recommended limit fixed by the World Health Organization) during 2017 and 2019.[6] The breakpoints of the regression lines between the distance from Lodi, SARS-CoV-2 cases and excess mortality in 38 Italian provinces of Lombardia, Emilia Romagna, Piemonte, Trentino Aldo Adige and Veneto was carried out by the *SegReg software* (available at: https://www.waterlog.info/segreg.htm). We called this metHod to derive the radius of 'red zOnes' to PrEvent the spread of future epidemics, as the HOPE method. In the breakpoint analysis, data were expressed as point estimate (the breakpoint) and 95% confidence block. The distance of each Italian province from the outbreak of infection was calculated by using the Google Mapping Technology, a system of recognized scientific validity.[7] The association between continuous variables was investigated by Pearson product moment correlation coefficient (r) and P values. Other calculations were performed by SPSS for Windows Version 22, Chicago, IL, USA.

Results

On 21 March 2020, the total SARS-CoV-2 cases (including active cases, recovered/discharge patients and deceased) in Italy were 53 578 over a total population of about 60 millions of inhabitants. In all Italian provinces ($n = 107$), there was a non-linear relationship between SARS-CoV-2 cases and the distance from Lodi and the deviation from uniformity mostly concerned the provinces of Lombardia and those of neighboring regions (Piemonte, Emilia Romagna, Trentino Alto Adige and Veneto) (figure 1—upper panel). In all Italian provinces ($n = 107$), no relationship was found between SARS-CoV-2 cases and population density (see Supplementary figure S1).

Radius of the red zone around Lodi which minimizes SARS-CoV-2 cases and excess mortality

In an analysis including the provinces of Lombardia and those of the four neighboring Regions ($n = 38$ provinces), the burden of SARS-CoV-2 cases increased dramatically when the distance from Lodi reduced below 92 km (95% confidence block: 81–119 km) (figure 1—bottom panel). When the same analysis was carried out according to the percent increase in all-cause mortality (figure 1 - bottom panel) the link between excess risk of mortality and distance from Lodi became steeper when the distance from the outbreak of Lodi reduced below 140 km (95% confidence block: 131–182 km). Thus, 92 and 140 km emerged as the radiuses of red zone around Lodi (95% confidence block for both outcomes: 81–182 km) which minimize SARS-CoV-2 cases and excess mortality, respectively, in neighboring provinces during the first phase of epidemic in Italy (figure 2). We also found that the prevalent cases of SARS-CoV-2 infection (collected up to 21 March 2020) were directly and strongly related to the concomitant excess death rate observed in the same 38 provinces ($r = 0.90$, $r^2 = 0.81$, $P < 0.001$), implying that 81% of the observed excess mortality is explained by SARS-CoV-2 cases (figure 3).

Effect modification by O_3 pollution

On univariate analysis, the mean values of days with $O_3 > 120\ \mu g/m^3$ during the past 3 years (2017–2019) were directly related to both prevalent cases of SARS-CoV-2 on 21 March ($r = 0.52$, $P = 0.001$) and excess all-cause mortality ($r = 0.57$, $P < 0.001$). We then analyzed whether air pollution amplified the relationship between the distance from Lodi of 38 provinces of five North Italian Regions, SARS-CoV-2 cases and excess mortality and we found that O_3 pollution significantly modified ($P < 0.005$) the strength of the relationship between distance from Lodi with both SARS-CoV-2 cases and excess mortality rate (figure 4). Indeed, when the distance from Lodi reduced by 50 km, the burden of SARS-CoV-2 increases by 0.15 cases per 10^4 inhabitants in provinces with relatively lower level of O_3 pollution and by 12.9 cases per 10^4 inhabitants in those with relatively higher level of O_3 pollution (effect modification, $P = 0.001$) (figure 4). Remarkably, the same effect modification was also found ($P = 0.005$) for the excess mortality rate (figure 4). In fact, a 50-km reduction in the distance from Lodi associated with 12.7% increase in excess mortality in provinces with relatively lower level of O_3 pollution and with 81.3% increase in the same outcome variable in provinces with relatively higher level of O_3 pollution. Thus, O_3 pollution modifies the relationship between the distance from Lodi, SARS-CoV-2 cases and excess all-cause mortality.

Use of swabs, distance from Lodi, SARS-CoV-2 cases and excess mortality rate

On 21 March 2020, the Veneto Region performed a higher number of swabs (109 per 10^4 inhabitants) as compared to those made in Trentino Alto Adige (73 per 10^4 inhabitants), Lombardia (66 per 10^4 inhabitants), Emilia Romagna (55 per 10^4 inhabitants) and Piemonte (25 per 10^4 inhabitants).[3] To assess whether the higher number of swabs made in Veneto associated with lower SARS CoV-2 cases and excess mortality as compared to those of other Regions independently from to the distance from Lodi, we can refer to the graph in figure 1 (bottom panels). This analysis showed that the number of SARS CoV-2 cases in provinces of Veneto did not materially differ from those found in other provinces of Piemonte, Emilia Romagna and Trentino Alto Adige (included Sondrio, which

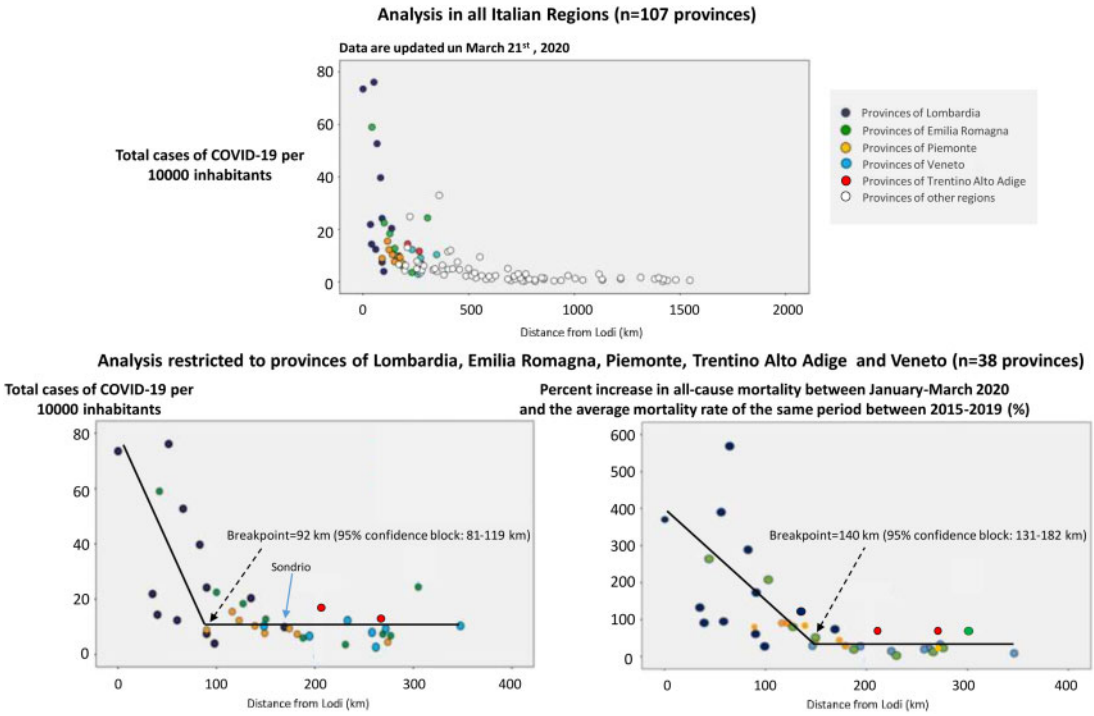

Figure 1 Upper panel: Relationship between distance from Lodi and SARS-CoV-2 cases in 107 Italian provinces on 21 March 2020. **Bottom panel, left**: relationship between distance from Lodi and total SARS-CoV-2 cases (at 21 March 2020) in the provinces ($n = 38$) of Lombardia, Emilia Romagna, Piemonte, Trentino Alto Adige and Veneto. **Bottom panel, right**: relationship between distance from Lodi and excess mortality in the provinces ($n = 38$) of Lombardia, Emilia Romagna, Piemonte, Trentino Alto Adige and Veneto

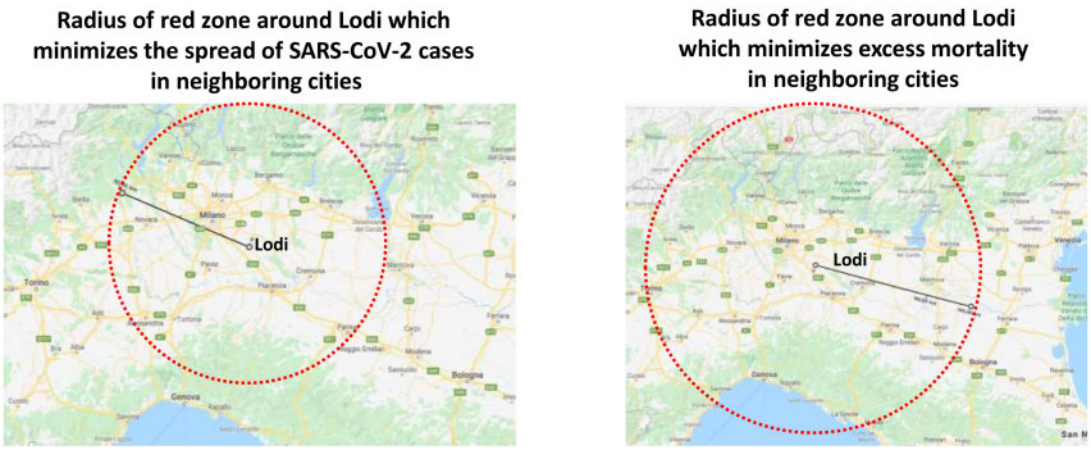

Figure 2 Radius of the red zone around the outbreak of Lodi which minimizes the spread of SARS-CoV-2 cases (on the left) and excess mortality (on the right) in neighboring cities. Of course, either within or outside the red zones, hand-washing, wearing masks and physical distancing remain as fundamental tools to fight COVID-19 dispersal

is located in Lombardia) when matched for the distance from Lodi. Similarly, in provinces of Veneto located >140 km far from Lodi, the excess mortality overlapped to that of provinces of Emilia Romagna and of two provinces of Piemonte, i.e. two regions in which the use of swabs was 50% and 77% lower, respectively, that those made in Veneto.

Discussion

This is the very first study describing a pragmatic method based on the breakpoint analysis to identify the radius of red zone minimizing the spread of SARS-CoV-2 and the excess mortality around an established outbreak of infection in a wide geographical area of a western country totalizing about 25 millions of inhabitants. Indeed, we found that a radius of 92–140 km (95% confidence block ranging from 81 to 182 km) around Lodi minimizes SARS-CoV-2 dispersal and excess mortality in the provinces of Lombardia and in those of neighboring regions during the first phase of epidemic in Italy and propose to apply such an approach to districts of other countries with an established outbreak of SARS-CoV-2 infection to assess generalizability. If confirmed in other studies, the HOPE method can offer a methodological basis to Health Authorities to circumscribe the red zones around an established outbreak of infection in other countries worldwide during future epidemics due to highly infective pathogens with an R_0 similar to that of SARS-CoV-2 ($2<R_0<4$).

We also found that O_3 pollution amplifies the strength of the relationship between distance from Lodi, SARS-CoV-2 cases and

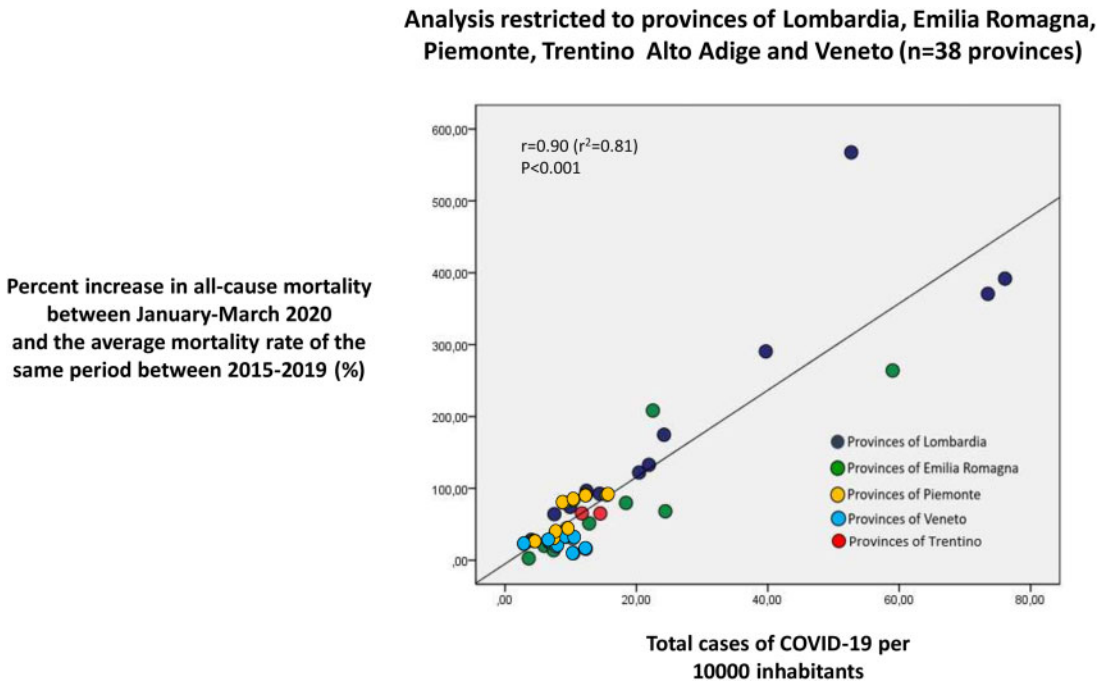

Figure 3 Association between SARS-CoV-2 cases on 21 March 2020 and excess mortality in 38 provinces of Lombardia and neighboring Regions (Lombardia, Emilia Romagna, Piemonte, Trentino Alto Adige and Veneto). See the label of Y axis for details

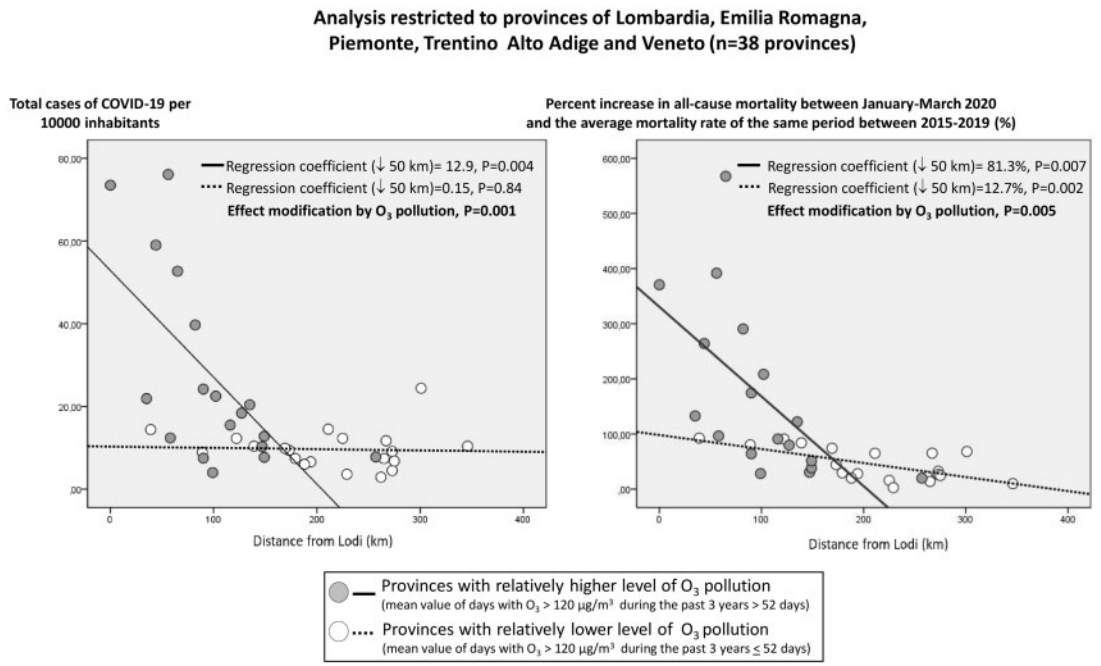

Figure 4 Effect modification by ozone (O_3) pollution on the relationship between distance from Lodi, total SARS-CoV-2 cases (**left**) and excess mortality (**right**) in the provinces of Lombardia, Emilia Romagna, Piemonte, Trentino Alto Adige and Veneto. Data are regression coefficient associated to a 50 km reduction in the distance from Lodi, and *P* values

excess mortality in Lombardia, Emilia Romagna, Trentino Alto Adige, Piemonte and Veneto. This observation is the first one reported in literature and it is of public health relevance because it indicates that the coexistence of O_3 pollution and nearness to an established outbreak of infection of SARS-CoV-2, plays a primary role in epidemic dispersal and associated excess mortality. O_3 pollution is a well-recognized environmental risk factor causing breathing problems and respiratory diseases and it is one of the regulated air pollutants with a recommended limit fixed by the World Health Organization. Our observations are germane to those reported in three previous papers.[2,8,9] In the paper by Coccia,[2] air pollution amplified the relationship between population density and SARS-CoV-2 cases in 55 Italian province capitals and in another paper by Fattorini,[8] it was reported that long-term air-quality data significantly correlated with cases of SARS-CoV-2 in up to 71 Italian provinces (updated 27 April 2020). In a recent paper by Zoran et al.,[9] a strong correlation was reported between COVID-19 cases and number of deaths with daily average ground level of O_3 in the city of Milan. The novelty of our study, with respect to that of Zoran et al.,[9] is that we face the problem of air pollution from a different

perspective, i.e. (i) by considering O_3 pollution as an effect modifier (and not only as a simple risk factor) in the relationship between the distance from the outbreak of infection (i.e. the city of Lodi), COVID-19 dispersal and excess mortality and (ii) by extending the analysis to a geographical area (including and not limited to the sole urban area of Milan) totalizing about 25 million of inhabitants. In the aggregate, our results provide further evidence that long-term exposure to atmospheric contamination represents a favorable factor for the spread of SARS-CoV-2 epidemic from an outbreak to neighboring cities as well as for the excess mortality rate observed during the first phase of epidemic, the latter being a finding which was not previously described. The role of air pollution as an effect modifier is further supported by the notion that the unique N-terminal fragment within the spike protein which characterizes viral genome allows the attachment of the virus on air pollutants. This interpretation is germane to that of Coccia[2] who suggests that the accelerated transmission of COVID-19 is mainly due to the mechanism of 'air pollution-to-human transmission'. Furthermore, there is also evidence that ozone per se induces lung inflammation through stimulation of the oxidative stress process thus exacerbating the health consequences of SARS-CoV-2 infection. Our hypothesis is that the coexistence between this mechanism(s) with the proximity between the cities to the outbreak of Lodi facilitates the spread of SARS-CoV-2 epidemic. Of course, we cannot exclude that other unmeasured polluting factors due to transports and industries can interact with population crowding to exacerbate COVID-19 dispersal. Another interesting observation emerged in our study is the strong association ($r = 0.90$) between SARS-CoV-2 cases (collected up to 21 March) and concomitant excess death rate observed in the 38 provinces of Lombardia and neighboring regions, implying that 81% of the observed excess mortality in those provinces is explained by the burden of SARS-CoV-2. Although 'association' does not imply 'causation', a correlation coefficient of 0.90 is strongly suggestive of a causal role of SARS-CoV-2 epidemic in the pathway leading to the excess mortality rate in Lombardia and neighboring regions between the first trimester 2020 and the corresponding trimesters of 2015–2019.

Furthermore, our study is also the first one investigating, by using regions as an instrumental variable, whether a public health intervention contemplating also a wider use of swabs could reduce the spread of SARS-CoV-2 infection and excess mortality in a wide geographical area including five regions in North Italy totalizing about 25 millions of inhabitants. In our study, by using regions as an instrumental variable,[10] we found that, at the beginning of the epidemic, the lower number of burden of SARS CoV-2 cases and the relatively lower excess mortality in the Veneto region with respect to the frequency of the same outcomes observed in the other provinces of Lombardia, Emilia Romagna, Trentino Alto Adige and Piemonte seems to be due to the higher distance from the original outbreak of infection (the city of Lodi) and lower O_3 pollution of the Veneto region rather than due to the more frequent use of swabs in the same region. However, the hypothesis that the wider use of swabs could prevent the dispersal and the public health consequences of SARS CoV-2 cases needs to be specifically confirmed in larger studies worldwide.

Our study presents some limitations. First, we did not test the external validity of the HOPE method in other countries. Thus, the generalizability of this method remains to be formally tested in future studies. Second, the data on O_3 pollution represent an aggregate of several days and therefore a granular analysis was not performed. Third, the public health utility of a wider use of swabs needs to be further investigated in specifically designed studies to definitely assess the utility of swabs for the containment of the epidemic. Fourth, given the ecological nature of our study, we cannot exclude the potential effect on the study results and interpretation of ecological fallacy, a type of bias that arises when an inference is made about an individual based on aggregate data.

In conclusion, to the best of our knowledge, this is the first study describing a pragmatic method to define the radiuses of the red zone during the SARS-CoV-2 epidemic around an established outbreak of infection minimizing the dispersal of infection and excess mortality in neighboring cities. We also found that the distance from the outbreak of infection (Lodi, placed in the Lombardia Region) and O_3 pollution plays a primary role to interpret the dispersal and the public health consequences (in terms of excess mortality) of SARS-CoV-2 in a wide geographical area in North Italy totalizing about 25 millions of inhabitants. Furthermore, given the fact that the district of Lodi is similar to other sites worldwide, the HOPE method we propose can be applied to other countries having similar characteristics in terms of industrialization, climate, and social interaction as Lodi and be useful to define the red zones in future epidemics due to highly infective pathogens with an R_0 similar to that of SARS-CoV-2 ($2 < R_0 < 4$). Finally, the creation of quarantine zones, by imposing a ban on the free movement of persons outside the radius of the restricted area, is of public health relevance because it avoids the dispersal of epidemic to neighboring places. A standardized analytical strategy such as that proposed by us (the HOPE method) to identify the radius of the red zones, together with the limitations to the free movement of persons also within the restricted area, allows the Health Authorities to trace the contacts of index cases by limiting the diffusion of epidemics and reduces the social and economic costs of a generalized lockdown.

Supplementary data

Supplementary data are available at *EURPUB* online.

Acknowledgments

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Conflicts of interest: None declared.

Key points

- The burden of SARS-CoV-2 cases and mortality increases when the distance of neighboring cities from the original outbreak of infection in Italy (that is, from the city of Lodi) reduces below 92 and 140 km, respectively.
- Ozone (O_3) pollution plays a primary role to modulate the relationships between the distance from the outbreak of infection, SARS-CoV-2 cases and mortality in a geographical area in North Italy totalizing about 25 million of inhabitants.
- Both the distance from the outbreak of infection and O_3 pollution should be taken into account to clarify the spreading of SARS-CoV-2 cases and mortality in the first phase of the epidemic in Italy as well as in future epidemics due to highly infective pathogens similar to SARS-CoV-2.

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Demographic and public health characteristics explain large part of variability in COVID-19 mortality across countries

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Background: The numbers of coronavirus disease 2019 (COVID-19) deaths per million people differ widely across countries. Often, the causal effects of interventions taken by authorities are unjustifiably concluded based on the comparison of pure mortalities in countries where interventions consisting different strategies have been taken. Moreover, the possible effects of other factors are only rarely considered. **Methods:** We used data from open databases (European Centre for Disease Prevention and Control, World Bank Open Data, The BCG World Atlas) and publications to develop a model that could largely explain the differences in cumulative mortality between countries using non-interventional (mostly socio-demographic) factors. **Results:** Statistically significant associations with the logarithmic COVID-19 mortality were found with the following: proportion of people aged 80 years and above, population density, proportion of urban population, gross domestic product, number of hospital beds per population, average temperature in March and incidence of tuberculosis. The final model could explain 67% of the variability. This finding could also be interpreted as follows: less than a third of the variability in logarithmic mortality differences could be modified by diverse non-pharmaceutical interventions ranging from case isolation to comprehensive measures, constituting case isolation, social distancing of the entire population and closure of schools and borders. **Conclusions:** In particular countries, the number of people who will die from COVID-19 is largely given by factors that cannot be drastically changed as an immediate reaction to the pandemic and authorities should focus on modifiable variables, e.g. the number of hospital beds.

Introduction

On 11 March 2020, the World Health Organization characterized coronavirus disease 2019 (COVID-19) as a pandemic with increasing deaths recorded globally. The numbers of deaths per million people across countries differ widely. Some risk factors that can explain this huge variability have been proposed: number of hospital beds per population,[1] Bacillus Calmette–Guérin (BCG) vaccination,[2] temperature,[3] age of the population[4] and frequency of comorbidities (e.g. hypertension[5] and diabetes[6]), with a strong association existing between these factors. On the other side are non-pharmacologic interventions that differ widely, from the use of efficacious face masks and case isolation to comprehensive measures constituting case isolation, social distancing of entire population and closure of schools and borders. The exact quantification of these factors across countries is nearly impossible, given the length of their action. Nonetheless, the causal effects of interventions taken by authorities are often unjustifiably concluded based on a comparison of pure mortalities in countries where interventions of different strategies have been taken.