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Assessing the impact of temperature and humidity exposures during early infection stages on case-fatality of COVID-19: A modelling study in Europe

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ABSTRACT

Background Although associations between key weather indicators (i.e. temperature and humidity) and COVID-19 mortality have been reported, the relationship between these exposures at different timings in early infection stages (from virus exposure up to a few days after symptom onset) and the probability of death after infection (also called case fatality rate, CFR) has yet to be determined.

Methods We estimated the instantaneous CFR of eight European countries using Bayesian inference in conjunction with stochastic transmission models, taking account of delays in reporting the number of newly confirmed cases and deaths. The exposure-lag-response associations between fatality rate and weather conditions to which patients were exposed at different timings were obtained using distributed lag nonlinear models coupled with mixed-effect models.

Results Our results show that the Odds Ratio (OR) of death is negatively associated with the temperature, with two maxima (OR = 1.29 (95% CI: 1.23, 1.35) at −0.1°C; OR = 1.12 (95% CI: 1.08, 1.16) at 0.1°C) occurring at the time of virus exposure and after symptom onset. Two minima (OR = 0.81 (95% CI: 0.71, 0.92) at 23.2°C; OR = 0.71 (95% CI: 0.63, 0.80) at 21.7°C) also occurred at these two distinct periods correspondingly. Low humidity (below 50%) during the early stages and high humidity (approximately 89%) after symptom onset were related to the lower fatality.

Conclusion Environmental conditions may affect not only the initial viral load when patients are exposed to the virus, but also individuals’ immune response around symptom onset. Warmer temperatures and higher humidity after symptom onset were linked to lower fatality.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic, attributable to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed unprecedented challenges to the world including many European countries. The number of deaths in Europe (1,116,017) counts for approximately 27% of all COVID-19 deaths worldwide (data accessed on July 17, 2021 (Our World in Data, 2021)). The relationship between weather conditions and COVID-19 fatality rates in Europe have not been fully determined. Furthermore, the impact of the weather conditions to which patients were exposed during the early infection stages (i.e. between virus infection and a few days after symptom onset) is unknown.

Temperature and humidity can likely influence the outcome of infection in two ways: affecting the initial viral load and modulating the immune response in patients. A possible distinction between these two mechanisms is the time point at which environmental risk factors take effect during the course of infection. The stability and the viability of SARS-CoV-2 are likely to be affected by environmental conditions when individuals are exposed to the virus (Chin et al., 2020). A higher initial viral load may pose a higher risk for developing severe diseases later. On the other hand, local innate immune responses in the upper or lower respiratory tract can be activated immediately after symptom onset (Schultze and Aschenbrenner, 2021). The dynamics of the response can be influenced by temperature or humidity (V’kovski et al., 2021; Courtney and Bax, 2021), presumably, during the time when it was activated.

According to the states of immune responses and pathogenesis, the infection course of SARS-CoV-2 can be divided into three stages:
asymptomatic incubation period, non-severe symptomatic period, and severe respiratory symptomatic stage (Shi et al., 2020). If certain controllable environmental conditions (e.g., temperature and humidity) during the non-severe symptomatic period can affect patients’ innate immune responses (Rintamaki, 2007; Andersson and Tracey, 2012; Vkovski et al., 2021) and hence their risk of death, preventive measures can be designed to reduce COVID-19 severity for these cases. However, until now, no such preventive measures are proposed because the impact of those conditions during the symptomatic period is unknown.

Although many studies have reported that low temperatures may increase the COVID-19 deaths or mortality (Sarkodie and Owusu, 2020; Ma et al., 2020; Benedetti et al., 2020; Jiang and Xu, 2020; Wu et al., 2020; Yuan et al., 2020), these studies did not have a direct measurement on the risk of death. Case fatality rate (CFR) (Khafaie and Rahim, 2020; Fan et al., 2021) is an important index to measure the disease severity, but one limitation is that this rate only represents the average proportion of deaths among all confirmed cases over a duration of time, without the ability to reflect the instantaneous probability of death. This time-varying instantaneous probability, also called instantaneous CFR (iCFR) (Ramos et al., 2021), can be influenced by many factors, such as change in health care capacity (Khan et al., 2020) and variations in weather conditions (Poddar et al., 2020; Orrt et al., 2021). Challenges exist in estimating the iCFR due to the time delays between confirming a positive case and reporting his/her outcome (Khafaie and Rahim, 2020; Newall et al., 2020). A more accurate estimation of the iCFR can be obtained if these delays are incorporated in modelling.

The study aimed at assessing the relationships between weather conditions COVID-19 patients were exposed to at different timings of the early infection course and their death risk. To resolve the above issues in delays and to estimate the iCFR, stochastic modelling (Endo et al., 2019) was used, taking into account of the delays in reporting the number of newly confirmed cases and deaths in each of the European countries. After adjusting delays in reporting cases and deaths, the correlation between the iCFR and daily weather conditions at different timings since the infection was obtained using distributed lag non-linear models (DLNMs) coupled with generalized linear mixed models.

2. Material and methods
2.1. Data collection

Our study focused on eight European countries (the United Kingdom, Italy, France, Spain, Germany, Netherlands, Sweden, and Romania) where the cumulative number of deaths was larger than 2000 during the first wave of the pandemic. The daily numbers of reported COVID-19 cases and deaths in these eight European countries from 16th February to 31st July 2020 were collected from ‘Our World in Data’ (Our World in Data, 2021). The community outbreak period was defined as beginning when the daily number of cases exceeded the country’s baseline (the 5% quantile of the maximal daily number of new cases) for two consecutive days and ending when the average case number was less than that baseline for two consecutive days.

Daily mean temperatures for the eight European countries and daily mean relative humidity values for five countries (Italy, Spain, Germany, Netherlands, and Sweden) were collected from the European Climate Assessment and Dataset (ECA&D) (European Climate Assessment and Dataset, 2021). For countries lacking relative humidity data (i.e. the United Kingdom, France, and Romania), we calculated relative humidity values using the ratio of the actual water vapor pressure divided by the saturation water vapor pressure (Wu et al., 2020) (see Supplementary Methods). In this study, the daily mean temperatures and relative humidity values for each country were calculated using the average records from all monitoring stations.

2.2. Estimating COVID-19 transmission patterns by SEIR model

We constructed a stochastic model that extended Susceptible-Exposed-Infectious-Recovered (SEIR) model to reproduce the COVID-19 transmission dynamic and estimate the iCFR and the effective reproduction number (Re) for each of countries during their outbreaks. The extended SEIR model contained three additional compartments: HR, hospital confirmed cases who later recovered; HD, hospital confirmed cases who later died of infection; and D, total deaths (Fig. 1). In order to calculate the iCFR of the date of case confirmation, newly confirmed cases were divided into HR and HD compartments following the probabilities of 1-iCFR and iCFR upon the date of case confirmation. Delays for case confirmation and death reporting were included. To estimate parameters in stochastic models, the Particle Markov chain Monte Carlo (PMCMC) method (Endo et al., 2019; Li et al., 2020), a combination of particle filtering and Markov chain Monte Carlo approaches was used (See Supplementary Methods). Posterior distributions of all parameters used in the model were obtained using the Nimble package in R (de Valpine et al., 2017) (version 3.6.1). The settings of prior distributions for these parameters were provided in Supplementary Methods.

2.3. Estimating the effects of temperature and relative humidity on the COVID-19 iCFR based on a DLNM model

In order to avoid the impacts from the variations in non-pharmaceutical interventions (NPIs) (Flaxman et al., 2020), we estimated the effects of weather conditions during the epidemic period when Re remained relatively stable below 1.5. Presumably, the variations of NPIs were assumed to be minor during this period.

To explore the non-linear relationship between weather conditions during the early infection stages and the iCFR, while taking account of other unknown local factors for each country, a combination of distributed lag nonlinear models (DLNMs) (Gasparrini, 2011) and generalized linear mixed models (GLMM) was adopted. For detailed steps, please see Supplementary Methods.

2.4. Model validation

To assess the convergence of parameters in the SEIR model, we constructed three independent chains of algorithm sets with 100,000 iterations and calculated the Gelman-Rubin convergence diagnostic statistics (Gelman and Rubin, 1992) across the three chains. For DLNM models, we used different combinations of temperature and relative humidity as predictors. The model with the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) was chosen as the best-fitting model. The prediction performance of the best-fitting model was presented by comparing its predicted iCFR with the iCFR calculated by SEIR models (Supplementary Figure 1).

3. Results

3.1. Case fatality in Europe

In order to estimate the iCFR among the eight European countries, we developed a stochastic epidemic model (See Method and Fig. 1A) taking account of delays between symptom onset and the confirmation of infection (i.e. confirmation delay) and delays between the confirmation and death (i.e. infection outcome delay). The model estimated the mean confirmation delays varied from 2.4 to 5.4 days, and the mean infection outcome delays varied from 7.9 to 12.4 days among these countries (Fig. 1B, Supplementary Table 1). Incorporating the variations of such delays allowed a more accurate estimation of the country-specific iCFR and hence its relationship with weather conditions.

Our model successfully captured the dynamics of the daily new cases and deaths during the first wave (Fig. 2, Supplementary Table 2). The epidemic patterns were similar (reaching a maximum of approximately
or over eighty cases per one million people per day in April) among most of the countries, except Sweden, and Romania. Generally, the daily maximum number of deaths occurred in April. Four countries (including the United Kingdom, Italy, France, and Spain; see Fig. 2A) had higher mortality rates (number of deaths per one million people): Spain had the highest daily estimated mortality rate of 18, followed by the United Kingdom 14, Italy 13, and France 11. The remaining countries (including Germany, Netherlands, Sweden and Romania; see Fig. 2B) demonstrated lower mortality rates during similar periods: Netherlands had the highest daily estimated mortality rate of 9, followed by Sweden 7, Germany 3 and Romania 2.

Generally, the estimated iCFRs in most of the countries decreased rapidly after reaching the maximum value in late March or early April and became more stable after then (Fig. 3); however, variations still exist. Among the four high mortality countries, iCFRs appeared to increase again slowly after reaching their minimum values (Fig. 3A): the rates increased again from the minimum values 0.12 to 0.14 in the United Kingdom; 0.11 to 0.13 in Italy; 0.18 to 0.20 in France; and 0.09 to 0.12 in Spain. iCFRs among low mortality countries generally demonstrated a decreasing trend or maintained at low values (Fig. 3B): the rates maintained between 0.05 and 0.06 in Germany; 0.07 and 0.08 in the Netherlands. In Sweden and Romania, after reaching their peaks in mid-April, the iCFR continued decreasing from 0.10 to 0.03 and from 0.07 to 0.03, respectively. In order to explore the association between weather conditions and the iCFR without the impacts of changes in NPIs, only the period when the value of Re remained below 1.5 was used. For most countries, Re reduced rapidly before April and fluctuated around 1 after then (Fig. 3).

3.2. Weather effects on iCFRs

Daily mean temperatures among these European countries gradually increased during the first wave of the pandemic (Fig. 4). Daily relative humidity in low mortality countries generally increased (Fig. 4B), but the increase was not clearly observed in high mortality countries (Fig. 4A). During the study period, the median of the daily mean temperatures ranged between 10.4°C and 16.5°C among the eight countries, and the median of the daily mean relative humidity ranged between 61.8% and 75.4% (Supplementary Table 3). Furthermore, most countries had temperatures ranging from 4°C to 20°C, and relative humidity ranged from 40% to 87%. The temperature changed the most in Sweden from -2°C to 21°C, and changed the least in Spain from 7°C to 20°C. Romania had the largest change in the relative humidity (i.e. 30%–87%), and Spain had the smallest (i.e. 63%–86%).

The DLNM model with both temperature and relative humidity as predictors was selected as the best-fitting model for assessing the effects of environmental conditions (see Methods, Supplementary Table 4 and Supplementary Table 5). Fig. 5B depicts the associations between temperatures and risk of death with a median temperature of 11°C as the reference. Lower temperatures, especially when temperatures were below 8°C, were more likely to increase COVID-19 iCFRs. We found that the estimated odds ratio (OR) of fatality peaked at virus exposure time.
when the temperature was low (OR = 1.29 (95% CI: 1.23, 1.35) at -0.1°C). However, surprisingly the OR reached a second peak value one day after symptom onset with similar temperature (OR = 1.12 (95% CI: 1.08, 1.16) at 0.1°C, see Fig. 5B). The lowest OR occurred at two days after symptom onset (OR = 0.71 (95% CI: 0.63, 0.80) at 21.7°C), and the second-lowest was observed at virus exposure time (OR = 0.81 (95% CI: 0.71, 0.92) at 23.2°C).

These results suggest that both the initial viral load during the virus exposure time, and the immune responses at approximately a few days after symptom onset were affected by environmental temperatures. For example, a decrease from 5°C to 0°C at one day after symptom onset was associated with an increased risk of deaths (OR increased from 1.03 to 1.07; see Fig. 5B). This increase was significantly greater than that during the presymptomatic transmission period at three days before symptom onset (OR only increased from 1.006 to 1.012).

The overall cumulative OR of temperature during the early infection stages was calculated by summing the effect of each time point between exposure to the virus and two days after symptom onset. A negative relationship between temperature and the OR of fatality was observed over the range of -2°C to 22°C (Fig. 5C). With exposure to a warm temperature of 24°C, the cumulative ORs during the first two days after symptom onset was 0.79. In order to check whether the results are caused by autocorrelation in weather, we further performed Fourier analysis. We found that temperature in Italy has a more distinct pattern.
of 7 or 8-day periodicity. There is no similar pattern in temperature among other countries or in relative humidity (Supplementary Figure 2).

Fig. 5D shows the associations between the humidity and risk of death, with a relative humidity of 62% as the reference. The highest OR (1.08, 95% CI: 1.07, 1.10) was observed at 79.6% relative humidity at symptom onset time. The cumulative OR increased when the humidity raised from 30% to 80%. However, the cumulative OR clearly reduced when the humidity increased from 80% to 89%. This reduction was associated with high humidity mainly after symptom onset (see Fig. 5D). The cumulative OR for the first two days after symptom onset was 0.66, with the exposure of relative humidity of 89%.

We checked the robustness of the estimated associations between weather conditions and the risks of death after re-fitting the model to data during different periods of time (i.e. from March to April, March to May, and March to June). In addition, to verify if the selected model is affected by the sample size, we re-fitted the model using smaller-size data sets (i.e. 5%, 10%, 15% and 20% of samples were removed from the full dataset). In both cases, we found that the effects of weather conditions on the risk of death were generally consistent (see Supplementary Figure 3 and Supplementary Figure 4).

Fig. 3. Model-estimated iCFR and Re in the eight European countries. (A) Daily iCFR and Re in countries where the mortality rates were relatively high. (B) Daily iCFR and Re in countries where the mortality rates were relatively low. Red and purple curves represent the estimated mean iCFR and Re, light red and dark red shaded areas represent the 95% and 50% credible intervals for iCFR. Purple shaded areas represent the 95% credible intervals for Re. The black vertical lines refer to the dates when Re reduced to below 1.5. iCFRs after these dates were used for estimating the effects of weather conditions. Daily mean iCFR, Re, and their credible intervals were obtained from the PMCMC posterior samples. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)
In summary, the variations of iCFRs within the eight European countries were associated with changes in weather conditions. Furthermore, the OR of fatality was clearly associated with the temperature and humidity that patients were exposed to at two distinct infection stages: virus exposure and after symptom onset.

4. Discussion

Although previous studies have explored the association between weather conditions (e.g. temperature and humidity) and COVID-19 deaths (Biktasheva, 2020; Li, 2020; Wu et al., 2020), it is still unknown how such conditions affect COVID-19 fatality risk during the infection progress. We found that the temperature and humidity were associated with the risk of death not only at virus exposure time but also after symptom onset (Fig. 5), which suggests that environmental conditions may influence both the initial viral load and an individual’s immune response to the virus (presumably through the innate immune system). These findings were obtained from distributed lag nonlinear models (Gasparrini, 2011) with the iCFR estimated using a stochastic disease transmission model that accounted for delays in infection confirmation and infection outcome.

During the first epidemic wave in Europe, certain countries suffered high mortality rates. We found that warm conditions were associated with reduced risk of deaths, especially when the temperature was greater than 15°C. Among the study countries, Romania showed a temperature warmer than this threshold for a long period of time (more than half of the study period). Sweden and Netherlands also showed a warmer temperature for several days. In addition, our results show that the risk of death was low when the relative humidity ranged below 50% (Fig. 5E). Germany and Romania had humidity below 50% for a longer time, which may be a possible reason to explain why they experienced lower iCFR. A negative relationship between the relative humidity and iCFR was observed when the humidity was larger than 80%. Our results may help explain diverging patterns among previous studies, namely that humidity and case fatality are negatively correlated in humid areas (Biktasheva, 2020), but positively correlated in dry regions (Li, 2020).
How extremely high humidity (>80% in Fig. 5E) can affect the severity of COVID-19 remains largely unknown. Low humidity has been previously found to make mice more susceptible to severe disease by impairing the function of mucosal barrier (Kudo et al., 2019). Similarly, a recent study proposed a hypothesis that the use of face masks is linked to the reduced severity of COVID-19 infections because the humidity of inspired air increases (Courtney and Bax, 2021). The beneficial effect of extremely high humidity (>80%) that was observed is likely due to a
similar mechanism. Mucus layers constitute a biochemical barrier to inhibit pathogen penetration (McAuley et al., 2017). A well-hydrated mucus layer ensures the continuous flow of mucus, responsible for removing pathogens from the airways and lungs (Moriyama et al., 2020).

Although the association between weather and COVID-19 related deaths has been previously reported (Biktasheva, 2020; Li, 2020; Wu et al., 2020), questions such as when (e.g. which infectious stage) and how these factors affect disease fatality have not been clarified. Many infected individuals, after being contact-traced or developing symptoms, are isolated at home or quarantine/isolation centers. We found that exposure to a warmer temperature (24°C) during the first two days after symptom onset was associated with a 19% reduction in the effect from the exposure to the reference temperature during the same time. Similarly, exposure to a higher relative humidity (89%) after symptom onset was associated with a 31% reduction in the effect from the exposure to the reference humidity level in the same period. Therefore, based on all these results, we recommend further evaluation of certain potential individual preventive measures for infected individuals, such as staying in a proper warm place after symptom onset especially in cold weather and wearing a face mask to increase the humidity of inspired air. Moreover, further epidemiological observational studies (e.g. case-control study) in different populations and environments are needed to determine optimal indoor environmental conditions that can reduce CFR most.

In addition to the evidence that low temperatures increase the stability and viability of the virus, inhalation of cold air at the initial virus exposure time, can make the upper airway more suitable for viral replication (Kang et al., 2021; V’kovski et al., 2021), resulting in large viral load, and potentially more severe adverse outcomes. On the other hand, how the temperature that patients were exposed to after symptom onset can affect immune responses is still unclear. This can be explained by some hypotheses of innate immunity. Macrophages, which produce cytokines and chemokines, have been found to increase in the lower airways after exposure to cold air (Larsson et al., 1998). IL-6 and TNF-α, the cytokines that play important roles in mediating SARS-CoV-2-associated cytokine storms (Hojyo et al., 2020; Copaescu et al., 2020), have been reported to increase after cold exposure (Rhind et al., 2001). The activation of these factors usually begins within a week after symptom onset (Schultze and Aschenbrenner, 2021). In general, vagus nerve circuits can regulate cytokines release in macrophages to prevent potentially damaging inflammation (Rosas-Ballina et al., 2011; Wang et al., 2003; Andersson and Tracey, 2012). Exposure to cold can affect physiological responses (Rintamaki, 2007), possibly including vagus or other immune-related activities. Overreaction of innate immunity may cause immune system dysregulation, leading to severe adverse outcomes (Zhang et al., 2021). These hypotheses of innate immunity suggest that there might be a link between temperature exposure in the early infection stages and COVID-19 disease severity.

Some limitations exist in this study. First, the effects of other interventions (e.g. increasing number of PCR tests performed and improvement of medical treatment) on the CFR were not considered. There are minor variations in the weekly number of COVID-19 tests conducted in the eight European countries during the study period (European Centre for Disease Prevention and Control, 2021). To avoid the effects caused by the variation of medical treatment and NPIs, we used the data during the first wave of the pandemic when the changes in interventions were minor (when Re was stable and near one). Second, the accuracy of indoor temperature and humidity data is not available. It is reasonable to believe that the house indoor temperature and humidity were largely affected by the weather in Europe where air conditioners or heaters were not frequently used at home during our study period. Thus, there is a monotonic relationship between house indoor condition and weather. Similarly, within-country variability of weather was not considered. Third, we cannot rule out the effect of certain confounding factors related to personal behaviours. (e.g. the dry air in winter can irritate people’s airways, which triggers more people to be cautious and reduce outdoor activities). In addition, because in some countries, many cases were confirmed and isolated in hospitals around two days after symptom onset on average (see Fig. 1B), hence their environmental exposure would mainly be determined by the hospital air conditioning system. Therefore, we only assess the impact of weather exposure no longer than that time.

Ethics approval

Ethics approval is not needed as the study uses publicly available country-level (aggregated) morbidity, mortality, and weather data.

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Data availability

Daily reported COVID-19 cases and deaths in these eight European countries from 16th February to 31st June 2020 were collected from ‘Our World in Data’ (https://github.com/owid/covid-19-data/tree/master/public-data). Daily weather data for the eight European countries were collected from the European Climate Assessment and Dataset (https://www.ecad.eu/) and United States National Oceanic and Atmospheric Administration (https://www.ncei.noaa.gov/access/search/data-search/global-summary-of-the-day). The data and materials are available from the corresponding author on reasonable request.

Author contributions

Hsiang-Yu Yuan and Jingbo Liang designed the study. Jingbo Liang collected, analyzed, and modelled the data. Jingbo Liang and Hsiang-Yu Yuan wrote the paper.

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.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envres.2022.112931.

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