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Covid-19-Linked Mortality in Continental France Administrative Areas Is Linked to a Weather Index

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Abstract

OBJECTIVE

To assess the effect of a weather index on in-hospital Covid-19-linked deaths.

DESIGN

Ecological study.

SETTING

Continental France administrative areas. The study period, from 18 March to 30 May 2020, corresponds to the main outbreak period in France.

POPULATION

Covid-19-linked in-hospital deaths.

MAIN OUTCOME MEASURES

In-hospital deaths and demographics (population, human density, male sex and population percentage >59 years old) were obtained from national and centralized public databases. County weather indexes were calculated by the French National Meteorological Agency.

RESULTS

Weather indicators and population density were factors independently associated with the Covid-19 death toll. Colder counties had significantly higher mortality rates ($P < .00001$). Percentages of males and population >59 years old in French counties did not affect Covid-19 in-hospital mortality.

CONCLUSIONS

Many parameters influence Covid-19-outbreak severity indicators. Human density is a strong factor but its exact importance is difficult to discern. Weather (mainly cold winter temperatures) was independently associated with mortality and could explain outbreak dynamics, which began and were initially more severe in the coldest counties of France. Weather partly explains fatality-rate discrepancies observed worldwide.

Strengths and limitations of this study

- In this ecological study (with data reliability, different climate zones, homogeneous social conduct during the outbreak), human density and weather index (related to cold temperatures during winter) independently influenced Covid-19 in-hospital mortality.
- In continental France, non-coastal counties and those with cold winters had significantly more in-hospital deaths.
- The coronavirus disease-2019 (Covid-19) pandemic is of multifactorial origin, and the impact of each etiological factor may vary among different countries and climes, therefore our results are mainly valid for temperate climes.

Introduction

The world is experiencing a major coronavirus disease-2019 (Covid-19) pandemic since December 2019, with >660,000 deaths (as of July 29). In France, the outbreak began in early March in Alsace "Département" (an administrative area comparable to a county in the US and UK; henceforth county), although probable cases were likely observed as early as November 2019 (in the same area) and quickly spread throughout continental France, with the major hotspot being Paris and its suburbs. The national lockdown, started 17 March, achieved flattening of the infection-outbreak curve (with the mortality peak reached on 6 April) and was eased on 11 May. Deaths exceed 30,000 and the virus is still circulating, although the outbreak seems to be under control since the end of May.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission causes Covid-19. All epidemics are the result of multiple factors, like human density, population displacements and individual human susceptibility (age, comorbidities,…). The question remains whether meteorological parameters are an independent factor of disease transmission and/or severity. Epidemiological studies are often biased by the imprecise results of large-scale biological testing, which has only recently been fully implemented in France. In-hospital deaths are more reliable data source, even though it encompasses different types of patients (some intensively treated, other just receiving palliative care).

This study was undertaken to explore the relationship between Covid-19-related in-hospital deaths, at the county level, and weather indicators.

Methods

Population

In this observational, ecological study, the relationship between in-hospital, Covid-19-linked mortality and climate zones in 94 continental French counties areas were analyzed. The overseas territories and Corsica were excluded from the analysis because of their particular localizations (with tropical or subtropical climate for some) and special insular conditions (for some). The study period lasted from 18 March to 30 May 2020.

Data

We compared the cumulative in-hospital death tolls in continental France (64 million inhabitants) by county to other factors (human density, climate, age and sex). The 18,314 deaths in France during the observation period classified by county were obtained from the French open-source database (*Santé Publique France*).[1] On 31 May and throughout June 2020, respectively, 35 and 888 additional in-hospital deaths were not considered for the study.

The following demographic characteristics were obtained from the French Institute for Statistics and Epidemiology (INSEE)[2] for each county: total population, percentage of the population >59 years, percentage of males in the population and density per km^2.

To assess the climate conditions, the French counties were classified according to a French Climate Rigor Index ('*Indice de Rigueur Climatique*').[3] That Index is calculated (from local measurements in each zone) by the French National Meteorological Agency. Three main climate patterns (H1, H2, H3) are defined according to winter temperatures, with H1 representing the coldest zone and H3 the warmest. Regional H2 zones are known to be homogeneous, which contrast with H1 zone, also subcharacterized according to summer temperatures and coastal influence into H1a, H1b, H1c (H1b being colder in winter and hotter in summer than H1a). These zones (Figure 1) are ranked according to winter temperatures from coldest to warmest: H1b>H1a>H1c>H2>H3. The data used were collected historically and are not from winter 2020.

Statistical Analyses

All database variables were tested. Bivariate statistical analyses were computed between in-hospital Covid-19-related mortality, and each weather indicator and each demographic parameter (density, age, sex). For comparisons, the Kruskal-Wallis test and Pearson's correlation test were used, as appropriate. The significance level was set at 5%. Those bivariate analyses were also completed by multivariate linear-regression analysis. The statistical quality of the model was assessed with the variance-covariance matrix of residuals and normality for their distribution. Outlier data were analyzed by Cook's distance which showed 3 counties with outlier data: Paris (which received patients from its suburbs because it has, as the nation's capital, a disproportionately high hospital density), Haut-Rhin and Belfort (where the outbreak began). Therefore, a second multivariate model excluding outliers was built; it had a more homogeneous distribution of residuals. The multivariate analysis was finalized by a multiple linear-regression model excluding outliers, with categorization of quantitative data into binary variables using the 3rd quartile as the threshold value. Finally, quantitative data were categorized into binary variables, in an attempt to characterize the effect size. The statistical analyses were computed with R software version 4.0.0.

Patient and public involvement

No patients were directly involved in this study.

Results

Demographic and hospital data characteristics during the study period are reported Table 1. The county characteristics according to climate zone are given in Table 2. Bivariate analysis demonstrated a significant link between in-hospital Covid-19-related mortality and climate zone (Figure 2A). Mean mortality rates for zones H1a, -b, -c, H2 and H3 differed significantly ($P = 8.84 \times 10^{-10}$). Bivariate analysis also found significant independent statistical links between Covid-19-linked mortality and population density or age >59 years but not male sex

(Table 3).

According to multivariate analysis (using H2 as the reference), Covid-19-linked mortality was associated with the following parameters: climate zones H1a and H1b, population density, and age. The results of the multiple linear-regression model excluding outliers (Figure 2B) were similar to those of the second model, with statistically significant effects of climate zones H1a and H1b and population density (Table 3). The only difference between this model and the previous one was the non-significance of the age. H3 climate zone and male sex were not significant in any of the 3 models constructed.

Discussion

Our results showed that Covid-19-related mortality is due, throughout continental France, to at least 2 independent factors: weather index and population density. We did not find a difference among counties for the percent population aged >59 years or male sex. As for any outbreak, the Covid-19 pandemic has multifactorial origins. Some are already well-documented: individual factors (age, male sex, comorbidities), high human-population density and all types of human displacements. Many others are still being discussed (climate, weather indicators, socioeconomic factors, immune status, …).

Individual risk factors for Covid-19 severity were identified relatively quickly, as this pathology often requires hospitalization (with or without ventilation), and it first emerged in developed countries. The main severity factors reported are: age >50 years, comorbidities, male sex.[4-6] Comorbidities are independent factors with a multivariable odds ratio (OR) ranging from 1.31 (diabetes) to 2.94 (pulmonary disease).[4] Age is a major independent factor, with a reported multivariable OR of 1.10 per 1-year increment[5] or 1.31 per 10-year increment[4] and male sex has an OR of 1.13. We attribute our inability to find an age effect among French counties to 2 reasons: first, only in-hospital deaths were available according to county and the oldest patients were not systematically hospitalized (while in-assisted-residence deaths account for one-third of the death toll in France). Therefore, the among-county differences for the >59-year-old class were not retrieved from the in-hospital death toll. Nevertheless, despite the significantly higher proportion of >59-year-olds in H1c, H2 and H3 climate zones (Table 2), in-hospital mortality was significantly higher in H1a categories. We did not find male sex to be discriminant among French counties, because they had a mean 48.4% of males with a small standard deviation of 0.5. Ethnicity[7] and socioeconomic status have also been also evoked as etiological factors but their independence remains to be proven.

For most epidemics, especially of respiratory diseases, population density is a major cause of transmission. Cities are more affected than rural areas, and within cities, neighborhoods with dense housing are unsurprisingly more affected. The highest death tolls were in big cities (New York, Paris, Madrid, London, …) and within them, poor neighborhoods were more severely affected for highly interwoven reasons. However, the 'number of people/land area' is a poor indicator of the human-population-density characteristic, as it is embedded in a wide variety of situations (housing mode, transportation mode, inner-city density, human interactions, cultural and behavioral habits,…). Indeed, many outbreaks occurred in (cruise or military) ships,[8] likely due to the same combined effect of closed environment and prolonged contact. Thus, the Diamond Princess cruise was classified among the most affected 'entities' at the beginning of the pandemic in March.[9] Somehow, cruise ships are the perfect laboratory model of outbreak spread in small cities. Our results showed that human density is an independent factor for Covid-19-linked deaths but we acknowledge that its exact importance cannot be determined, as we are limited by the wide range of situations that human-density encompasses, with many factors that should be taken into account. Our assessment of human density (and interactions) was mainly made during a lockdown, therefore the importance of this factor is likely underestimated herein. Also, human density does not have the same connotation and consequences in poor and rich countries. The outbreak extension to hot climates indicates that human interactions are likely even more important for the virus spread than weather (unlike our results).

The cities gather not only locals but also draws infected people, with airport arrivals representing the fastest entry point of the outbreak. Since the 1968-69 flu pandemic, we have known that international travel and plane transportation is a major vector of virus displacement. According to Liu et al,[10] Covid-19 has spread in multiple major cities in China that have huge numbers of inbound and outbound passengers. They used an internet-based ("Baidu") migration scale index for 30 cities and found an association with confirmed cases. Indeed, population migration and displacement or movement-control measures implemented (quarantine, limited migration/limited travel/travel bans, closed borders) reduced virus spread everywhere. In 2019, the top 5 countries receiving international tourists were France, Spain, Italy, China and the USA. With the exception of China (whose death tolls are subject to question), those countries were the main ones affected by the pandemic during March-April. This human-migration dynamic partly explains the epidemic's temporality worldwide. Some human behaviors (hand-shaking, cheek-kissing, body contact, crowds, …), intrinsically responsible for social-distancing differences, are also likely to influence SARS-Cov-2 transmission. But, within a small- or medium-sized country (as in France), they may be relatively homogeneous. It is difficult to individualize these cultural factors, and no clear and unbiased study indicators have been identified, but they likely account for mortality discrepancies among countries. For example, massive virus spreading was reported after carnivals in different settings (New Orleans in Louisiana, Gangelt in Germany,[11] …).

Viral epidemics, such flu and gastroenteritis, are known to follow seasonal cycles with resurgences during autumn and winter, favored by cold temperatures. Previous coronavirus outbreaks (SARS-CoV-1 and MERS) were also linked to weather[10] (mainly temperature). A climate effect on the wide-dissemination of a respiratory disease is a highly intuitive conclusion and SARS-CoV-2 is transmitted mainly through droplets and aerosols. Temperature, humidity and wind were found to impact the spread of this outbreak,[10,12-14] based on confirmed infections. Notably, biological testing is known to monitor imprecisely this outbreak because 23%-40% of the cases are asymptomatic.[15] Moreover, false-negative reverse transcriptase-polymerase chain reaction results may occur. Therefore, our study focused on more precise, in-hospital deaths, collected in a centralized electronic database.

In many countries spanning multiple latitudes, clear north-south gradients were observed with more deaths further north: France, Spain, Italy, USA (as of July 27, Illinois had proportionally 2.2 more deaths than Florida, despite Florida has the highest percentage in the US of population > 65 years old). Notably, Rome, the largest Italian city with a Mediterranean climate, was proportionally less affected than northern cities, which has a different climate.

Based on our results for continental France, southern and coastal areas seem to be more protected than colder inland areas. Indeed, our results were confirmed by the observations in Spain, where Madrid region was hit harder than coastal and southern zones. Western Europe (France, UK, Belgium, Netherlands and Germany) has a mainly oceanic climate and, indeed, the outbreak followed the same course (sudden rise in March and decline in May), despite their different public health policy approaches. Also, few large cities in East and Southeast Asia (except Wuhan) were Covid-19 pandemic hotspots, despite human density being among the highest in the world. That observation can be explained by 3 categories of factors: 1) aggressive management of the epidemic in cold areas (South Korea, Japan, China implemented the strictest lockdown in the world), 2) other protective behaviors, including traditional cultural distancing, 3) some protective climate effect in warm areas (Hong Kong, Singapore, Taiwan,…). Of course, the combination of these 3 factors would achieve the highest protection.

However, the climate's protective effect alone would not spare a population from the outbreak and, indeed, almost all countries on earth have been impacted. Moreover, the protection afforded by higher temperatures remains to be precisely defined depending on the climate, because the interactions among temperature, humidity, wind and sunlight are complex. Still, Prata et al[16] showed that, in Brazil, the climate's effect exists even in tropical regions, where the range of temperatures is limited. The weather effect may also be supported by the massive infections observed in climatized facilities, in meat processing facilities (in USA,[17] France, and Germany) or in boats,[8] but many confounding factors may be involved. Air pollution also was shown to be associated with virus spread in northern Italy,[18] but pollution is closely related to weather conditions, therefore its independent role is still to precise.

Public health strategies have been extensively implemented worldwide.[19] It is likely that climate alone is not sufficient to extinguish this outbreak and public health interventions, aimed at containing and reducing virus circulation, will be needed on a long-term basis. Both weather factors and human social behaviors (partly linked to meteorological conditions) seem to contribute to Covid-19 epidemiological dynamics. This multifactorial character explains why some warm countries in Central and South America are experiencing massive epidemics (Brazil, Mexico), despite some climate protection, because their national strategies implement only partial social distancing and, even now, are somehow opposing it. Liu et al[10] concluded rightly for China: "this epidemic will be faded to a large degree in the coming warmer season with the enforcement of public health interventions in China," which emphasizes the absolute need for social-distancing and not to rely solely on a weather effect.

Strengths and Limitations

Few countries have simultaneous hospital-data reliability, different climate zones, homogeneous social conduct during the outbreak (including a uniformly implemented lockdown) and high Covid-19-related mortality. France met all those conditions. However, our study has some limitations. First, the death-toll breakdown per county is available only for in-hospital deaths. Second, the impact of each etiological factor may vary among different countries and climes, therefore our results are mainly valid for temperate countries in the northern hemisphere. Third, the France weather index we used provided a historic collection of weather data, but not winter 2019-2020 conditions.

Conclusion

Our findings suggest that climate is an independent factor influencing Covid-19-linked mortality at the country level in France. Human-population density (and therefore social interactions) is an independent factor, whose impact has been widely proven. These factors, along with others (age pyramid, cultural factors, …), explain the course of this pandemic throughout the world. The fatality discrepancies among countries, and among administrative subdivisions within countries, likely follow the same rules worldwide. Our findings also imply that next winter will likely see resurgent Covid-19 outbreaks, but seasonality is complex, as it involves more than climate alone (immune status, virus mutation, …).

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Table 1. French County Demographics and Covid-19–Linked Death Data

Parameter	Mean	SD	95% CI	Median (1st -3rd quartile)
Population	686736.9	520296.7	[580169.8-793304.0]	543636.5 (306500.5-887016.7)
In-hospital deaths	194.8	288.1	[135.8-253.8]	80.5 (34.5-191)
In-hospital death rate*	24.1	23.2	[19.4-28.9]	14.1 (8.6-33.8)
Density (inhabitants/km²)	575.8	2471.9	[69.51082.1]	85.4 (51.6-165.9)
Age >59 y (%)	29.5	4.8	[28.5-30.5]	29.4 (26.4-33.2)
Male sex (%)	48.4	0.5	[48.3-48.5]	48.5 (48.1-48.8)

*Number per 100 000 inhabitants.

Table 2. Demographic and Covid-19–Linked Deaths Data According to Climate Zone

Climate zone	Counties, No. (%)	Population, mean	Population, density mean*	Age >59 y mean (%)	Male sex, mean (%)	In-hospital deaths, mean	In-hospital death rate**, mean
Zone H1a	18 (19)	1193507.1	2583.9	24.1	48.4	517.3	39.2
Zone H1b	15 (16)	473311.2	100.8	29.4	48.7	258.3	51.2
Zone H1c	18 (19)	551782.5	105.1	30.1	48.5	120.5	18.3
Zone H2	36 (38)	529843.7	80.4	31.6	48.4	50.6	10.2
Zone H3	7 (7)	994859.8	187.6	31.0	47.7	161.7	14.0

*Inhabitants/land area
**Number per 100 000 inhabitants.

Table 3. Statistical Analyses of In-Hospital Death Rates: Bivariate Analysis then Multivariate Analysis (Multiple-Linear Regression Excluding Outliers with Categorized Quantitative Data)

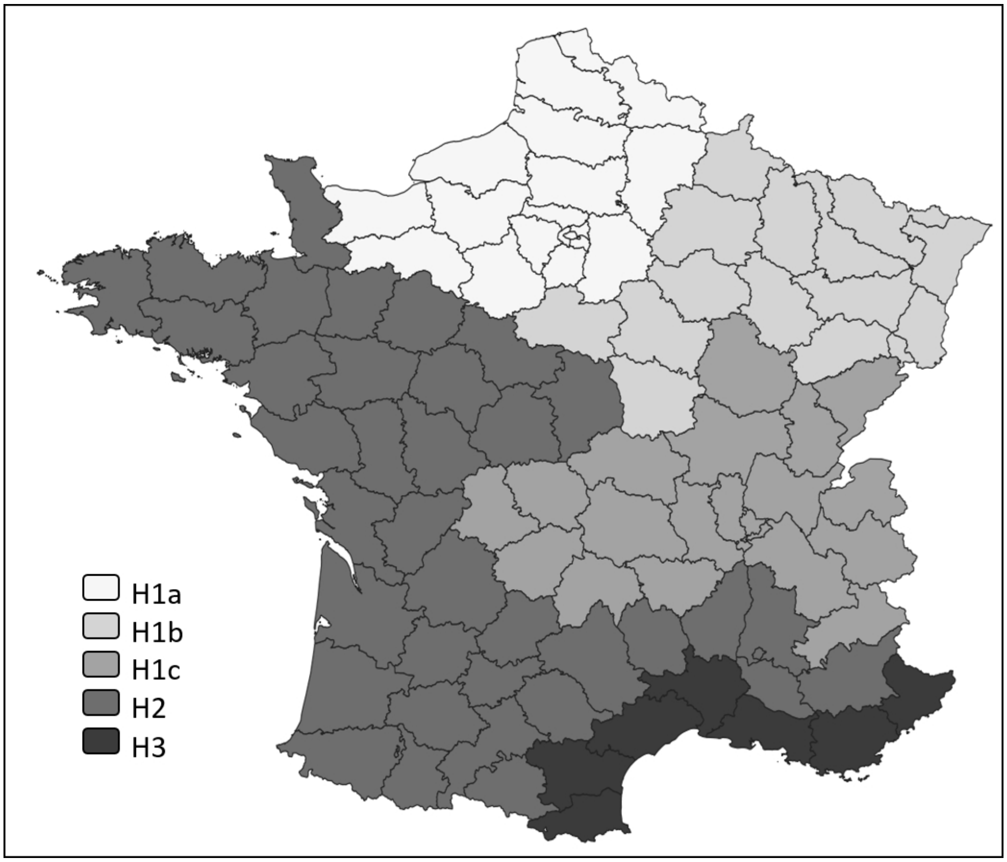
Factor	Statistical test	In-hospital mortality rate* Mean	Median	Correlation coefficient	*P* value
Bivariate Analysis					
Zone H1a	Kruskall-Wallis	39.2	37.6	–	8.84×10^{-10}
Zone H1b		51.2	46.6	–	
Zone H1c		18.3	14.3	–	
Zone H2		10.2	8.1	–	
Zone H3		14.0	12.2	–	
Density	Pearson's correlation	–	–	0.39	9.42×10^{-5}
Age >59 y, %		–	–	–0.45	5.36×10^{-6}
Multivariate Analysis (reference Zone H2)				Regression Coefficient [95% CI]	*P* value
Zone H1a				20.8 [12.0 to 29.6]	1.21×10^{-5}
Zone H1b				30.1 [21.3 to 38.9]	2.41×10^{-9}
Zone H1c				7.0 [–0.5 to 14.7]	0.074
Zone H3				–1.4 [–13.1 to 10.1]	0.803
Density >3rd quartile				8.5 [0.6 to 16.4]	0.0361
Age >59 y >3rd quartile				–3.8 [–10.6 to 2.9]	0.272
Male sex, % >3rd quartile				–2.5 [–8.4 to 3.3]	0.399

*Number per 100 000 inhabitants.

Figure legends

Figure 1. Main Climate Zones (H1a, H1b, H1c, H2, H3) of Continental France Administrative Areas ("Départements").

Figure 2. Boxplots of In-Hospital Mortality Rates According to the Main Climate Zones (A). The internal bold horizontal line is the median; the lower and upper box limits are the 5th and 95th percentiles, respectively; and the T-bars represent range. Multivariate linear-regression analysis (B) (95% confidence intervals CI; with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.



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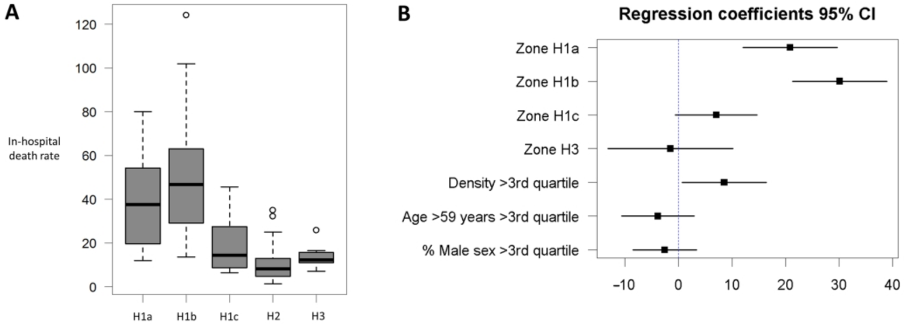

Figure 2. Boxplots of In-Hospital Mortality Rates According to the Main Climate Zones (A). The internal bold horizontal line is the median; the lower and upper box limits are the 1st and 3rd quartile, respectively; and the T-bars represent range. Multivariate linear-regression analysis (B) (95% confidence intervals CI; with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	**Recommendation**	**Page No**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 7, 16, 17

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

COVID-19–related in-hospital mortality in continental France administrative areas is linked to weather: an ecological study

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COVID-19–related in-hospital mortality in continental France administrative areas is linked to weather: an ecological study

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ABSTRACT

Objective To assess the effect of a weather index on in-hospital COVID-19–linked deaths.

Design Ecological study.

Setting Continental France administrative areas (*départements*; henceforth counties). The study period, from 18 March to 30 May 2020, corresponds to the main first outbreak period in France.

Population COVID-19–linked in-hospital deaths.

Main outcome measures In-hospital deaths and demographics (population, human density, male sex and population percentage >59 years old) were obtained from national and centralised public databases. County weather indexes were calculated by the French National Meteorological Agency.

Methods In this observational, ecological study, the relationship between in-hospital COVID-19–related mortality and climate zones in continental French counties were analysed, by comparing the cumulative in-hospital death tolls in France by county to other factors (population density, climate, age and sex). The study period lasted from 18 March to 30 May 2020. A multivariate linear-regression analysis of in-hospital mortality included climate zones, population density, population >59 years old and percentages of males as potential predictors. The significance level was set at 5%.

Results Weather indicators and population density were factors independently associated with the COVID-19 death toll. Colder counties had significantly higher mortality rates ($p<0.00001$). Percentages of males and population >59 years old in counties did not affect COVID-19 in-hospital mortality.

Conclusions Many parameters influence COVID-19 outbreak-severity indicators. Population density is a strong factor but its exact importance is difficult to discern. Weather (mainly cold winter temperatures) was independently associated with mortality and could help explain

outbreak dynamics, which began and were initially more severe in the coldest counties of continental France. Weather partly explains fatality-rate discrepancies observed worldwide.

Strengths and limitations of this study

- This ecological study is based on a country with data reliability, different climate zones and homogeneous social conduct during the study period.
- French continental administrative areas include coastal, non-coastal and other counties with cold winters.
- Climate, as a new independent factor, should be included in predictive modelisation of COVID-19 outbreaks.
- Generalisability of our results is mainly valid for temperate climates.
- Due to the ecological design of the study, we were unable to control for co-morbidities in the multivariate analysis.

INTRODUCTION

The world is experiencing a major novel coronavirus disease-2019 (COVID-19) pandemic since December 2019, with >1 570 000 deaths (as of 10 December 2020).[1] In France, the outbreak began in early March 2020 in the Alsace "*Département*" (an administrative area comparable to a county in the US and UK; henceforth county), quickly spread throughout continental France, with the major hotspot being Paris and its suburbs.[2] The national lockdown, started 17 March 2020, achieved flattening of the infection-outbreak curve (with the mortality peak reached on 6 April) and was eased on 11 May 2020.[2] Deaths exceeded 30 000 during the first wave and, although the outbreak seemed to be under control during the summer, a second wave started in October 2020.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission causes COVID-19. All epidemics are the result of multiple factors, like population density, human displacements and individual human susceptibility (age, co-morbidities, etc.). The question remains whether meteorological parameters are an independent factor of disease transmission and/or severity. Epidemiological studies are often biased by the imprecise results of large-scale biological testing, which has only recently been fully implemented in France. In-hospital deaths are a more reliable data source, even though it encompasses different types of patients (some intensively treated, other just receiving palliative care).

This study was undertaken to explore the relationship between COVID-19-linked in-hospital deaths, at the county level, and weather indicators.

METHODS

Population

In this observational, ecological study, the relationship between in-hospital, COVID-19–linked mortality and climate zones in 94 continental French counties areas was analysed. The overseas territories and Corsica were excluded from the analysis because of their particular localisations (with tropical or subtropical climate for some) and special insular conditions (for some). The study period lasted from 18 March to 30 May 2020.

Data

We compared the cumulative in-hospital death tolls in continental France (64 million inhabitants) by county to other factors (population density, climate, age and sex). The 18 314 deaths in France during the observation period classified by county were obtained from the French open-source database (*Santé Publique France*).[3] On 31 May and throughout June

2020, respectively, 35 and 888 additional in-hospital deaths were not considered for the study. In France, access to healthcare is free and during this outbreak, there was no shortage of available conventional or ICU hospital beds. In-hospital deaths in France are assigned to the areas where the deceased persons lived.

The following demographic characteristics for each county were obtained from the French Institute for Statistics and Epidemiology (INSEE)[4]: total population, percentage of the population >59 years (INSEE categorises oldest populations in only two classes: 60–74 and ≥75 years old), percentage of males in the population and human density per km^2.

To assess the climate conditions, the French counties were classified according to a French Climate Severity Index (*Indice de Rigueur Climatique*).[5] That Index is calculated (from local measurements in each zone) by the French National Meteorological Agency. Three main climate patterns (H1, H2, H3; figure 1) are defined according to winter temperatures, with H1 representing the coldest zone and H3 the warmest. Regional H2 zones are known to be homogeneous, which contrasts with H1 zones, sub-characterised according to summer temperatures and coastal influence into H1a, H1b, H1c (with H1b being colder in winter and hotter in summer than H1a). These zones are ranked according to winter temperatures from coldest to warmest: H1b>H1a>H1c>H2>H3. The data used were collected historically and are not from winter 2020.

Statistical Analyses

All database variables were tested. Bivariate analyses were computed between in-hospital COVID-19–related mortality, and each weather indicator and each demographic parameter (density, age, sex). For comparisons, the Kruskal–Wallis test and Pearson's correlation test were used, as appropriate. The significance level was set at 5%. Those bivariate analyses were also completed by multivariate linear-regression analysis (first multivariate model). The statistical quality of the model was assessed with the variance–covariance matrix of residuals and normality for their distribution. Data were analysed by Cook's distance, which showed three counties with outliers: Paris (which received patients from its suburbs because, as the nation's capital, it has a disproportionately higher hospital density), Haut-Rhin and Belfort (eastern France, where the outbreak began). Therefore, a second multivariate model excluding outliers was built, which had a more homogeneous distribution of residuals. The multivariate analysis was finalised by a multiple linear-regression model excluding outliers, with categorisation of quantitative data into binary variables using the third quartile as the threshold value (third model). The statistical analyses were computed with R software version 4.0.0.

Patient and public involvement

No patients were directly involved in this study.

RESULTS

Demographic and hospital data characteristics during the study period are reported **table 1**.

Table 1 French county demographic and COVID-19–linked mortality data

Parameter	**Mean**	**SD**	**95% CI**	**Median (1st–3rd quartile)**
Population	686 736.9	520 296.7	[580 169.8–793 304.0]	543 636.5 (306 500.5–887 016.7)
In-hospital deaths	194.8	288.1	[135.8–253.8]	80.5 (34.5–191)
In-hospital death rate*	24.1	23.2	[19.4–28.9]	14.1 (8.6–33.8)
Population density (inhabitants/km²)	575.8	2471.9	[69.5–1082.1]	85.4 (51.6–165.9)
Age >59 years (%)	29.5	4.8	[28.5–30.5]	29.4 (26.4–33.2)
Male sex (%)	48.4	0.5	[48.3–48.5]	48.5 (48.1-48.8)

*Number per 100 000 inhabitants.

SD, standard deviation; CI, confidence interval

Bivariate analysis demonstrated a significant link between in-hospital COVID-19-related mortality and climate zone (figure 2A**).** Mean (standard deviation) mortality rates for climate zones H1a (table 2), H1b, H1c, H2 and H3 differed significantly ($p=8.84\times10^{-10}$).

Table 2 French demographic and COVID-19–linked mortality data according to climate zone

Climate zone	Counties, No. (%)	Population, mean	Population, density mean*	Age >59 y mean (%)	Male sex, mean (%)	In-hospital deaths, mean	In-hospital death rate†, mean (SD)
H1a	18 (19)	1 193 507.1	2583.9	24.1	48.4	517.3	39.2 (21.8)
H1b	15 (16)	473 311.2	100.8	29.4	48.7	258.3	51.2 (31.4)
H1c	18 (19)	551 782.5	105.1	30.1	48.5	120.5	18.3 (11.8)
H2	36 (38)	529 843.7	80.4	31.6	48.4	50.6	10.2 (8.2)
H3	7 (7)	994 859.8	187.6	31.0	47.7	161.7	14.0 (6.0)

*Inhabitants/land area.

†Number per 100 000 inhabitants.

SD, standard deviation.

Bivariate analysis (correlation coefficients) also found significant independent statistical links between COVID-19-related mortality and population density or age >59 years but not male sex (table 3).

Table 3 Bivariate and multivariate analyses of in-hospital death rates*

Factor	In-hospital mortality rate† Mean (SD)	In-hospital mortality rate† Median (IQR)	Correlation coefficient	p value
Bivariate Analysis				
Zone H1a‡	39.2 (21.8)	37.6 (32.9–)	–	8.84×10^{-10}
Zone H1b‡	51.2 (31.4)	46.6 (34.0–)	–	
Zone H1c‡	18.3 (11.8)	14.3 (17.2–)	–	

Zone H2‡	10.2 (8.2)	8.1 (7.9–)	–	
Zone H3‡	14.0 (6.0)	12.2 (4.7–)	–	
Population density§	–	–	0.39	9.42×10^{-5}
Age >59 years, %§	–	–	–0.45	5.36×10^{-6}
Multivariate Analysis (reference zone H2)			**Regression coefficient [95% CI]**	
Zone H1a			20.8 [12.0 to 29.6]	1.21×10^{-5}
Zone H1b			30.1 [21.3 to 38.9]	2.41×10^{-9}
Zone H1c			7.0 [–0.5 to 14.7]	0.074
Zone H3			–1.4 [–13.1 to 10.1]	0.803
Population density >3rd quartile			8.5 [0.6 to 16.4]	0.0361
Age >59 years >3rd quartile			–3.8 [–10.6 to 2.9]	0.272
Male sex, % >3rd quartile			–2.5 [–8.4 to 3.3]	0.399

*Multiple-linear regression excluding outliers with categorised quantitative data.

†Number per 100 000 inhabitants.

‡Kruskall–Wallis test.

§Pearson's correlation test.

SD, standard deviation; IQR, interquartile range, 1st–3rd quartile.

According to multivariate analysis of the initial data (using zone H2 as the reference), COVID-19-linked mortality was associated with the following parameters: climate zones H1a (regression coefficient 14.6, p=0.00962) and H1b (regression coefficient 37.2, $p=4.39\times10^{-11}$), population density (regression coefficient 0.003, p=0.000229) and age (regression coefficient –0.97, p=0.0208) (supplemental appendix 1). Results of the multiple linear-regression model excluding outliers (Cook's distance >0.1) were similar, with statistically significant effects for climate zones H1a (regression coefficient 15.2, p=0.000785) and H1b (regression coefficient 30.4, $p=7.65\times10^{-11}$), population density (regression coefficient 0.004, p=0.00028) and age (regression coefficient -0.6, p=0.0404) (supplemental appendix 2). Residual analyses for the multivariate models using the initial data was less conclusive than that excluding outliers. After categorisation of quantitative data into binary variables, results remained similar with statistically significant effects of climate zones H1a and H1b and population density (table 3) (Figure 2B). The only difference between the third model and the second model was the non-significance of the age. H3 climate zone and male sex were not significant in any of the three models constructed.

DISCUSSION

Our results showed that COVID-19–related in-hospital mortality—throughout continental France—was due to at least two independent factors: weather index and population density. We did not find a difference among counties for the percent population aged >59 years or male sex. As for any outbreak, the COVID-19 pandemic has multifactorial origins. Some are already well-documented: individual factors (age, male sex, co-morbidities), high population density and all types of human displacements. Many others are still being discussed (weather indicators, socio-economic factors, immune status).

Individual risk factors for COVID-19 severity were identified relatively quickly, as this pathology often requires hospitalisation (with or without ventilation), and it first emerged in developed countries, after Wuhan, China. The main severity factors reported are: age >50 years, co-morbidities, male sex.[6-8] Co-morbidities are independent factors with a multivariable odds ratio (OR) ranging from 1.31 (diabetes) to 2.94 (pulmonary disease).[6] Age is a major independent factor, with a reported multivariable OR of 1.10 per 1-year increment[7] or 1.31 per 10-year increment[6] and male sex has an OR of 1.13. We attribute our inability to find an age effect among French counties to: first, only in-hospital deaths were available according to county and, second, the oldest patients were not systematically hospitalised (while in-assisted-residence deaths accounted for one-third of the death toll in

France). Therefore, the among-county differences for those >59-year-old–class deaths were not retrieved from the in-hospital death data. Nevertheless, despite the significantly higher proportion of >59-year-olds in H1c, H2 and H3 climate zones (table 2), in-hospital mortality was significantly higher in H1a zones.

We did not find male sex to be discriminant among French counties, because they had a mean 48.4% of males with a small standard deviation of 0.5. Ethnicity[9] and socio-economic status have also been evoked as etiological factors but their independence remains to be proven.

For most epidemics, especially of respiratory diseases, population density is a major cause of transmission. Cities are more affected than rural areas and, within cities, neighbourhoods with dense housing are, unsurprisingly, more affected. The highest death tolls were in big cities (New York, Paris, Madrid, London) and within them, poor neighbourhoods were more severely affected for highly interwoven reasons. However, the 'number of people/land area' is a poor indicator of the human-population–density characteristic, as it is embedded in a wide variety of situations (housing mode, transportation mode, inner-city density, human interactions, cultural and behavioural habits). Indeed, many outbreaks occurred on (cruise or military) ships,[10] likely due to the same combined effect of closed environment and prolonged contact. Thus, the Diamond Princess cruise was classified among the most affected 'entities' at the beginning of the pandemic in March 2020.[11] That said, cruise ships are the perfect laboratory model of outbreak spread in small cities.

Our results showed human density to be an independent factor for COVID-19–related deaths but we acknowledge that its exact importance cannot be determined, as we are limited by the wide range of situations that human density encompasses, with many factors that should be taken into account. Our assessment of human density (and interactions) was mainly made during a lockdown; therefore, the importance of this factor is likely underestimated herein. Also, population density does not have the same connotation and consequences in poor and rich countries. The outbreak extension to hot climates indicates that human interactions are likely even more important for virus spread than weather (unlike our results).

The cities gather not only locals but also draws infected people, with airport arrivals representing the fastest entry point of the outbreak. Since the 1968–69 flu pandemic, we have known that international travel and plane transportation is a major vector of virus displacement. According to Liu *et al*,[12] COVID-19 has spread in multiple major cities in China that have large numbers of inbound and outbound passengers. They used an internet-based ("Baidu") Migration Scale Index for 30 cities and found an association with confirmed cases. Pertinently, population migration and displacement or movement-control measures implemented (quarantine, limited migration/limited travel/travel bans, closed borders) reduced virus spread everywhere. In 2019, the top five countries receiving international tourists were France, Spain, Italy, China and the USA. Those countries were the main ones affected by the pandemic during March and April 2020. This human-migration dynamic partly explains the epidemic's temporality worldwide.[13]

Some human behaviours (hand-shaking, cheek-kissing, body contact, crowds), intrinsically responsible for social-distancing differences, are also likely to influence SARS-Cov-2 transmission. But, within a small- or medium-sized country (as in France), they may be relatively homogeneous. It is difficult to individualise these cultural factors, and no clear and unbiased study indicators have been identified, but they likely account for mortality discrepancies among countries. For example, massive virus spreading was reported after carnivals in different settings (New Orleans, Louisiana, and Gangelt, Germany[14]).

Viral epidemics, such flu and gastroenteritis, are known to follow seasonal cycles with resurgences during autumn and winter, favoured by cold temperatures. Previous coronavirus outbreaks (SARS-CoV-1 and Middle East Respiratory Syndrome) were also linked to weather[12] (mainly temperature). A climate effect on the wide dissemination of a respiratory disease is a highly intuitive conclusion and SARS-CoV-2 is transmitted mainly through droplets and aerosols. Temperature, humidity and wind were found to impact the spread of this outbreak,[12, 15-19] based on confirmed infections. Notably, biological testing is known to monitor imprecisely this outbreak because 23%–40% of the cases are asymptomatic.[20] Moreover, false-negative reverse transcriptase-polymerase chain reaction results may occur. Therefore, our study focused on more precise, in-hospital deaths, collected in a centralised electronic database.

In many countries spanning multiple latitudes, clear north–south gradients[18, 19] were observed with more deaths further north: France, Spain, Italy, USA (as of 10 December 2020, New York State had more deaths (35 183) than Florida (19 462),[1] despite Florida having a larger population and the highest percentage population in the US >65 years old). Notably, Rome, the largest Italian city with a Mediterranean climate, was proportionally less affected than northern cities,[19] which have a different climate.

Based on our results for continental France, southern and coastal areas seem to be more protected than colder inland areas. Notably, our findings were confirmed by observations made in Spain, where the Madrid region was hit harder than coastal and southern zones. Western Europe (France, UK, Belgium, Netherlands and Germany) has a mainly oceanic climate and the outbreak followed the same course (sudden rise in March, decline in May and resumption in October 2020),[1] despite their different public health-policy approaches. Also, few large cities in East and Southeast Asia (except Wuhan) were COVID-19 pandemic hotspots, despite human-population density being among the highest in the world. That observation can be explained by: (1) aggressive management of the epidemic in cold areas (South Korea, Japan, and China, which implemented the strictest lockdown in the world); (2) other protective behaviours, including traditional cultural distancing; (3) some protective climate effect in warm areas (Hong Kong, Singapore, Taiwan). Of course, the combination of these three factors would achieve the highest protection.

Pertinently, the climate's protective effect alone would not spare a population from the outbreak and, indeed, almost all countries on earth have been impacted. Moreover, the protection afforded by higher temperatures remains to be precisely defined depending on the climate, because the interactions among temperature, humidity, wind and sunlight are complex. Still, Prata *et al*[21] showed that, in Brazil, the climate's effect may exist, even in tropical regions, where the range of temperatures is limited. Inversely, the results of Hallal *et al*'s [22] nationwide antibody-prevalence survey in Brazil showed that the most affected areas were located along the Amazon river, which has the warmest climate. They explained those findings by human density on boats, the major means of transporting people, and excess multifactorial risks among indigenous populations.

Air pollution also was shown to be associated with virus spread in northern Italy,[23] but because pollution is closely related to weather conditions, its independent role remains to be specified.

Public health strategies have been extensively implemented worldwide.[24] It is likely that climate alone is not sufficient to extinguish this outbreak, and public health interventions, aimed at containing and reducing virus circulation, will be needed on a long-term basis. Weather factors and human social behaviours (partly linked to meteorological conditions) seem to contribute to COVID-19 epidemiological dynamics. This multifactorial character could explain why, despite some climate protection, some warm areas in Central and South America are experiencing massive epidemics. Notably, their national strategies implemented only partial social distancing and, even now, persist in opposing it (Brazil,[22] Mexico). Liu *et al*[12] concluded rightly for China: "this epidemic will be faded to a large degree in the coming warmer season with the enforcement of public health interventions in China," which emphasises the absolute need for social distancing and not to rely solely on a weather effect.

Strengths and Limitations

Few countries have simultaneous hospital-data reliability, different climate zones, homogeneous social behaviour during the outbreak (including a uniformly implemented lockdown) and high COVID-19-related mortality. France met all those conditions. However, our study has some limitations. First, the death-toll breakdown per county is available only for in-hospital deaths. Second, the impact of each etiological factor may vary among different countries and climates, therefore, generalisability of our results is mainly valid for temperate countries in the northern hemisphere. Third, the France weather index we used provided a historic collection of weather data, but not winter 2019–2020 conditions. Finally, co-morbidities could not be analysed because of the ecological design of the study but we think that their distribution is relatively homogeneous among French counties.

Conclusion

Our findings suggest that climate is an independent factor influencing COVID-19-linked mortality at the county level in continental France. Human-population density (and therefore social interactions) is an independent factor, whose impact has been widely proven. These factors, along with others (age pyramid, cultural factors, co-morbidities), explain the course of this pandemic throughout the world. The fatality discrepancies among countries and among administrative subdivisions within countries likely follow the same rules worldwide. Our findings also imply that this COVID-19 outbreak will last throughout the coldest periods, but seasonality is complex, as it involves more than climate alone (eg, immune status, virus mutation).

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Figure legends

Figure 1 Main climate zones (H1a, H1b, H1c, H2, H3) of continental France counties (“*départements*”).

Figure 2 (A) Boxplots of in-hospital mortality rates according to the main climate zones. The internal bold horizontal line is the median; the lower and upper box limits are the 1st and 3rd quartile, respectively; and the T-bars represent range. (B) Multivariate linear-regression analysis (95% confidence intervals (CI); with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.

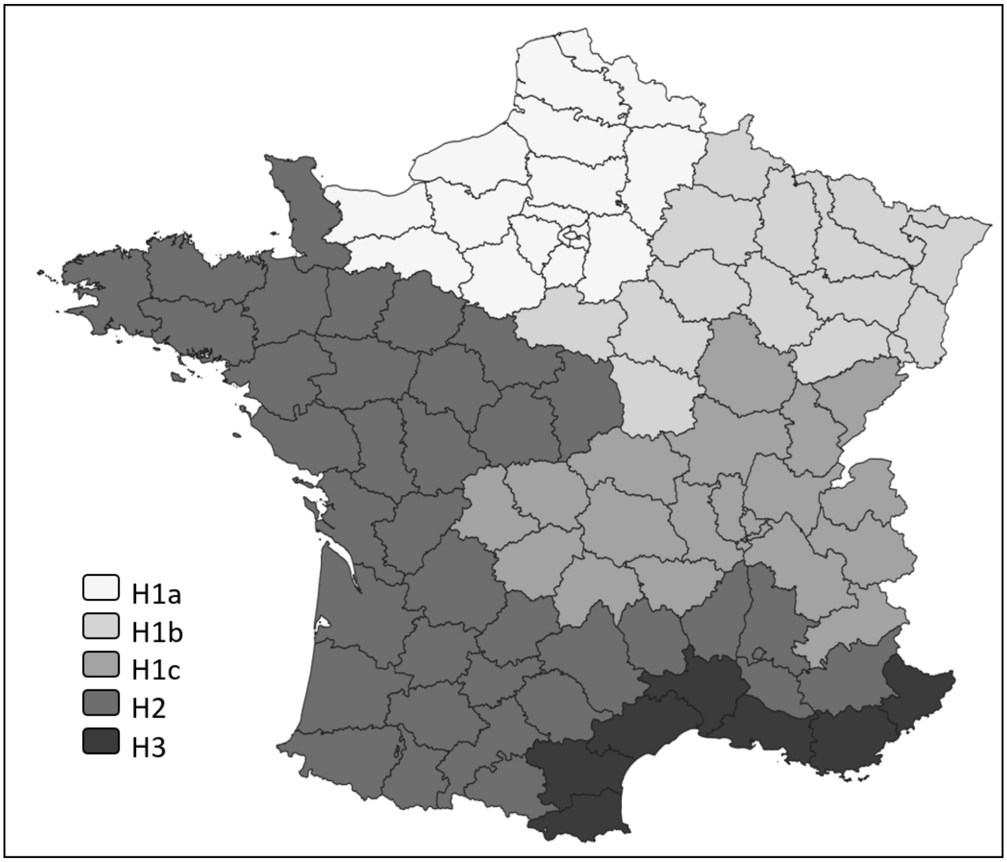

Figure 1. Main Climate Zones (H1a, H1b, H1c, H2, H3) of Continental France Administrative Areas ("Départements").

Figure 2. Boxplots of In-Hospital Mortality Rates According to the Main Climate Zones (A). The internal bold horizontal line is the median; the lower and upper box limits are the 1st and 3rd quartile, respectively; and the T-bars represent range. Multivariate linear-regression analysis (B) (95% confidence intervals CI; with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.

Supplemental material

Appendix 1 Multivariate multiple-linear regression analysis of initial data

Factor (reference zone H2)	Regression coefficient [95% CI]	p value
Zone H1a	14.6 [3.8 to 25.4]	0.00962
Zone H1b	37.2 [27.6 to 46.9]	4.39×10^{-11}
Zone H1c	6.0 [–2.7 to 14.9]	0.183
Zone H3	6.9 [–6.9 to 20.8]	0.329
Population density >3rd quartile	0.003 [0.001 to 0.004]	0.000229
Age >59 y >3rd quartile	–0.97 [–1.7 to –0.1]	0.0208
Male sex, % >3rd quartile	5.2 [–2.5 to 13.1]	0.187

Appendix 2 Multivariate multiple-linear regression analysis excluding outliers

Factor (reference zone H2)	Regression coefficient [95% CI]	p value
Zone H1a	15.2 [6.6 to 23.8]	0.000785
Zone H1b	30.4 [22.1 to 37.9]	7.65×10^{-11}
Zone H1c	6.8 [–0.1 to 13.8]	0.0574
Zone H3	3.4 [–7.5 to 14.4]	0.539
Population density >3rd quartile	0.004 [0.002 to 0.006]	0.00028
Age >59 years >3rd quartile	–0.6 [–1.3 to –0.04]	0.0404
Male sex, % >3rd quartile	0.6 [–5.6 to 6.9]	0.838

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 7, 16, 17

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Link between COVID-19–related in-hospital mortality in continental France administrative areas and weather: an ecological study

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Link between COVID-19–related in-hospital mortality in continental France administrative areas and weather: an ecological study

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Keywords: COVID-19, outbreak, pandemic, risk factors, weather

Word count: 2504

ABSTRACT

Objective To assess the effect of a weather index on in-hospital COVID-19–linked deaths.

Design Ecological study.

Setting Continental France administrative areas (*départements*; henceforth counties). The study period, from 18 March to 30 May 2020, corresponds to the main first outbreak period in France.

Population COVID-19–linked in-hospital deaths.

Main outcome measures In-hospital deaths and demographics (population, human density, male sex and population percentage >59 years old) were obtained from national and centralised public databases. County weather indexes were calculated by the French National Meteorological Agency.

Methods In this observational, ecological study, the relationship between in-hospital COVID-19–related mortality and climate zones in continental French counties were analysed, by comparing the cumulative in-hospital death tolls in France by county to other factors (population density, climate, age and sex). The study period lasted from 18 March to 30 May 2020. A multivariate linear-regression analysis of in-hospital mortality included climate zones, population density, population >59 years old and percentages of males as potential predictors. The significance level was set at 5%.

Results Weather indicators and population density were factors independently associated with the COVID-19 death toll. Colder counties had significantly higher mortality rates ($p<0.00001$). Percentages of males and population >59 years old in counties did not affect COVID-19 in-hospital mortality.

Conclusions Many parameters influence COVID-19 outbreak-severity indicators. Population density is a strong factor but its exact importance is difficult to discern. Weather (mainly cold winter temperatures) was independently associated with mortality and could help explain

outbreak dynamics, which began and were initially more severe in the coldest counties of continental France. Weather partly explains fatality-rate discrepancies observed worldwide.

Strengths and limitations of this study

- This ecological study is based on a country with data reliability, different climate zones and homogeneous social conduct during the study period.
- French continental administrative areas include coastal, non-coastal and other counties with cold winters.
- Generalisability of our results is mainly valid for temperate climates.
- Due to the ecological design of the study, we were unable to control for co-morbidities in the multivariate analysis.

INTRODUCTION

The world is experiencing a major novel coronavirus disease-2019 (COVID-19) pandemic since December 2019, with >1 570 000 deaths (as of 10 December 2020).[1] In France, the outbreak began in early March 2020 in the Alsace "*Département*" (an administrative area comparable to a county in the US and UK; henceforth county), quickly spread throughout continental France, with the major hotspot being Paris and its suburbs.[2] The national lockdown, started 17 March 2020, achieved flattening of the infection-outbreak curve (with the mortality peak reached on 6 April) and was eased on 11 May 2020.[2] Deaths exceeded 30 000 during the first wave and, although the outbreak seemed to be under control during the summer, a second wave started in October 2020.

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) transmission causes

COVID-19. All epidemics are the result of multiple factors, like population density, human displacements and individual human susceptibility (age, co-morbidities, etc.). The question remains whether meteorological parameters are an independent factor of disease transmission and/or severity. Epidemiological studies are often biased by the imprecise results of large-scale biological testing, which has only recently been fully implemented in France. In-hospital deaths are a more reliable data source, even though it encompasses different types of patients (some intensively treated, other just receiving palliative care).

This study was undertaken to explore the relationship between COVID-19-linked in-hospital deaths, at the county level, and weather indicators.

METHODS

Population

In this observational, ecological study, the relationship between in-hospital, COVID-19–linked mortality and climate zones in 94 continental French counties areas was analysed. The overseas territories and Corsica were excluded from the analysis because of their particular localisations (with tropical or subtropical climate for some) and special insular conditions (for some). The study period lasted from 18 March to 30 May 2020.

Data

We compared the cumulative in-hospital death tolls in continental France (64 million inhabitants) by county to other factors (population density, climate, age and sex). The 18 314 deaths in France during the observation period classified by county were obtained from the French open-source database (*Santé Publique France*).[3] On 31 May and throughout June 2020, respectively, 35 and 888 additional in-hospital deaths were not considered for the study. In France, access to healthcare is free and during this outbreak, there was no shortage of available conventional or ICU hospital beds. In-hospital deaths in France are assigned to the areas where the deceased persons lived.

The following demographic characteristics for each county were obtained from the French Institute for Statistics and Epidemiology (INSEE)[4]: total population, percentage of the population >59 years (INSEE categorises oldest populations in only two classes: 60–74 and ≥75 years old), percentage of males in the population and human density per km^2.

To assess the climate conditions, the French counties were classified according to a French Climate Severity Index (*Indice de Rigueur Climatique*).[5] That Index is calculated (from local measurements in each zone) by the French National Meteorological Agency. Three main climate patterns (H1, H2, H3; figure 1) are defined according to winter temperatures, with H1 representing the coldest zone and H3 the warmest. Regional H2 zones are known to be homogeneous, which contrasts with H1 zones, sub-characterised according to summer temperatures and coastal influence into H1a, H1b, H1c (with H1b being colder in winter and hotter in summer than H1a). These zones are ranked according to winter temperatures from coldest to warmest: H1b>H1a>H1c>H2>H3. The data used were collected historically and are not from winter 2020.

Patient and public involvement

No patients were directly involved in this study.

Statistical Analyses

All database variables were tested. Bivariate analyses were computed between in-hospital COVID-19–related mortality, and each weather indicator and each demographic parameter (density, age, sex). For comparisons, the Kruskal–Wallis test and Pearson’s correlation test were used, as appropriate. The significance level was set at 5%. Those bivariate analyses were also completed by multivariate linear-regression analysis (first multivariate model). The statistical quality of the model was assessed with the variance–covariance matrix of residuals and normality for their distribution. Data were analysed by Cook's distance, which showed three counties with outliers: Paris (which received patients from its suburbs because, as the nation's capital, it has a disproportionately higher hospital density), Haut-Rhin and Belfort (eastern France, where the outbreak began). Therefore, a second multivariate model excluding outliers was built, which had a more homogeneous distribution of residuals. The multivariate analysis was finalised by a multiple linear-regression model excluding outliers, with categorisation of quantitative data into binary variables using the third quartile as the threshold value (third model). The statistical analyses were computed with R software version 4.0.0.

RESULTS

Demographic and hospital data characteristics during the study period are reported **table 1**.

Table 1 French county demographic and COVID-19–linked mortality data

Parameter	Mean	SD	95% CI	Median (1st–3rd quartile)
Population	686 736.9	520 296.7	[580 169.8–793 304.0]	543 636.5 (306 500.5–887 016.7)
In-hospital deaths	194.8	288.1	[135.8–253.8]	80.5 (34.5–191)
In-hospital death rate*	24.1	23.2	[19.4–28.9]	14.1 (8.6–33.8)
Population density (inhabitants/km²)	575.8	2471.9	[69.5–1082.1]	85.4 (51.6–165.9)
Age >59 years (%)	29.5	4.8	[28.5–30.5]	29.4 (26.4–33.2)
Male sex (%)	48.4	0.5	[48.3–48.5]	48.5 (48.1-48.8)

*Number per 100 000 inhabitants.

SD, standard deviation; CI, confidence interval

Bivariate analysis demonstrated a significant link between in-hospital COVID-19-related mortality and climate zone (figure 2A**).** Mean (standard deviation) mortality rates for climate zones H1a (table 2), H1b, H1c, H2 and H3 differed significantly ($p=8.84\times10^{-10}$).

Table 2 French demographic and COVID-19–linked mortality data according to climate zone

Climate zone	Counties, No. (%)	Population, mean	Population, density mean*	Age >59 y mean (%)	Male sex, mean (%)	In-hospital deaths, mean	In-hospital death rate†, mean (SD)
H1a	18 (19)	1 193 507.1	2583.9	24.1	48.4	517.3	39.2 (21.8)
H1b	15 (16)	473 311.2	100.8	29.4	48.7	258.3	51.2 (31.4)
H1c	18 (19)	551 782.5	105.1	30.1	48.5	120.5	18.3 (11.8)
H2	36 (38)	529 843.7	80.4	31.6	48.4	50.6	10.2 (8.2)
H3	7 (7)	994 859.8	187.6	31.0	47.7	161.7	14.0 (6.0)

*Inhabitants/land area.

†Number per 100 000 inhabitants.

SD, standard deviation.

Bivariate analysis (correlation coefficients) also found significant independent statistical links between COVID-19-related mortality and population density or age >59 years but not male sex (table 3).

Table 3 Bivariate and multivariate analyses of in-hospital death rates*

Factor	In-hospital mortality rate† Mean (SD)	In-hospital mortality rate† Median (IQR)	Correlation coefficient	p value
Bivariate Analysis				
Zone H1a‡	39.2 (21.8)	37.6 (32.9–)	–	8.84×10^{-10}
Zone H1b‡	51.2 (31.4)	46.6 (34.0–)	–	
Zone H1c‡	18.3 (11.8)	14.3 (17.2–)	–	
Zone H2‡	10.2 (8.2)	8.1 (7.9–)	–	
Zone H3‡	14.0 (6.0)	12.2 (4.7–)	–	

Population density§	–	–	0.39	9.42×10^{-5}
Age >59 years, %§	–	–	–0.45	5.36×10^{-6}
Multivariate Analysis (reference zone H2)			**Regression coefficient [95% CI]**	
Zone H1a			20.8 [12.0 to 29.6]	1.21×10^{-5}
Zone H1b			30.1 [21.3 to 38.9]	2.41×10^{-9}
Zone H1c			7.0 [–0.5 to 14.7]	0.074
Zone H3			–1.4 [–13.1 to 10.1]	0.803
Population density >3rd quartile			8.5 [0.6 to 16.4]	0.0361
Age >59 years >3rd quartile			–3.8 [–10.6 to 2.9]	0.272
Male sex, % >3rd quartile			–2.5 [–8.4 to 3.3]	0.399

*Multiple-linear regression excluding outliers with categorised quantitative data.

†Number per 100 000 inhabitants.

‡Kruskall–Wallis test.

§Pearson's correlation test.

SD, standard deviation; IQR, interquartile range, 1st–3rd quartile.

According to multivariate analysis of the initial data (using zone H2 as the reference), COVID-19-linked mortality was associated with the following parameters: climate zones H1a (regression coefficient 14.6, p=0.00962) and H1b (regression coefficient 37.2, $p=4.39\times10^{-11}$), population density (regression coefficient 0.003, p=0.000229) and age (regression coefficient –0.97, p=0.0208) (supplemental appendix 1). Results of the multiple linear-regression model excluding outliers (Cook's distance >0.1) were similar, with statistically significant effects for climate zones H1a (regression coefficient 15.2, p=0.000785) and H1b (regression coefficient 30.4, $p=7.65\times10^{-11}$), population density (regression coefficient 0.004, p=0.00028) and age (regression coefficient -0.6, p=0.0404) (supplemental appendix 2). Residual analyses for the multivariate models using the initial data was less conclusive than that excluding outliers. After categorisation of quantitative data into binary variables, results remained similar with statistically significant effects of climate zones H1a and H1b and population density (table 3) (Figure 2B). The only difference between the third model and the second model was the non-significance of the age. H3 climate zone and male sex were not significant in any of the three models constructed.

DISCUSSION

Our results showed that COVID-19–related in-hospital mortality—throughout continental France—was due to at least two independent factors: weather index and population density. We did not find a difference among counties for the percent population aged >59 years or male sex. As for any outbreak, the COVID-19 pandemic has multifactorial origins. Some are already well-documented: individual factors (age, male sex, co-morbidities), high population density and all types of human displacements. Many others are still being discussed (weather indicators, socio-economic factors, immune status).

Individual risk factors for COVID-19 severity were identified relatively quickly, as this pathology often requires hospitalisation (with or without ventilation), and it first emerged in developed countries, after Wuhan, China. The main severity factors reported are: age >50 years, co-morbidities, male sex.[6-8] Co-morbidities are independent factors with a multivariable odds ratio (OR) ranging from 1.31 (diabetes) to 2.94 (pulmonary disease).[6] Age is a major independent factor, with a reported multivariable OR of 1.10 per 1-year increment[7] or 1.31 per 10-year increment[6] and male sex has an OR of 1.13. We attribute our inability to find an age effect among French counties to: first, only in-hospital deaths were available according to county and, second, the oldest patients were not systematically hospitalised (while in-assisted-residence deaths accounted for one-third of the death toll in France). Therefore, the among-county differences for those >59-year-old–class deaths were not retrieved from the in-hospital death data. Nevertheless, despite the significantly higher proportion of >59-year-olds in H1c, H2 and H3 climate zones (table 2), in-hospital mortality was significantly higher in H1a zones.

We did not find male sex to be discriminant among French counties, because they had a mean 48.4% of males with a small standard deviation of 0.5. Ethnicity[9] and socio-economic status have also been evoked as etiological factors but their independence remains to be proven.

For most epidemics, especially of respiratory diseases, population density is a major cause of transmission. Cities are more affected than rural areas and, within cities, neighbourhoods with dense housing are, unsurprisingly, more affected. The highest death tolls were in big cities (New York, Paris, Madrid, London) and within them, poor neighbourhoods were more severely affected for highly interwoven reasons. However, the 'number of people/land area' is a poor indicator of the human-population–density characteristic, as it is embedded in a wide variety of situations (housing mode, transportation mode, inner-city density, human interactions, cultural and behavioural habits). Indeed, many outbreaks occurred on (cruise or military) ships,[10] likely due to the same combined effect of closed environment and prolonged contact. Thus, the Diamond Princess cruise was classified among the most affected 'entities' at the beginning of the pandemic in March 2020.[11] That said, cruise ships are the perfect laboratory model of outbreak spread in small cities.

Our results showed human density to be an independent factor for COVID-19–related deaths but we acknowledge that its exact importance cannot be determined, as we are limited by the wide range of situations that human density encompasses, with many factors that should be taken into account. Our assessment of human density (and interactions) was mainly made during a lockdown; therefore, the importance of this factor is likely underestimated herein. Also, population density does not have the same connotation and consequences in poor and rich countries. The outbreak extension to hot climates indicates that human interactions are likely even more important for virus spread than weather (unlike our results).

The cities gather not only locals but also draws infected people, with airport arrivals representing the fastest entry point of the outbreak. Since the 1968–69 flu pandemic, we have known that international travel and plane transportation is a major vector of virus displacement. According to Liu *et al*,[12] COVID-19 has spread in multiple major cities in China that have large numbers of inbound and outbound passengers. They used an internet-based ("Baidu") Migration Scale Index for 30 cities and found an association with confirmed cases. Pertinently, population migration and displacement or movement-control measures implemented (quarantine, limited migration/limited travel/travel bans, closed borders) reduced virus spread everywhere. In 2019, the top five countries receiving international tourists were France, Spain, Italy, China and the USA. Those countries were the main ones affected by the pandemic during March and April 2020. This human-migration dynamic partly explains the epidemic's temporality worldwide.[13]

Some human behaviours (hand-shaking, cheek-kissing, body contact, crowds), intrinsically responsible for social-distancing differences, are also likely to influence SARS-Cov-2 transmission. But, within a small- or medium-sized country (as in France), they may be relatively homogeneous. It is difficult to individualise these cultural factors, and no clear and unbiased study indicators have been identified, but they likely account for mortality discrepancies among countries. For example, massive virus spreading was reported after carnivals in different settings (New Orleans, Louisiana, and Gangelt, Germany[14]).

Viral epidemics, such flu and gastroenteritis, are known to follow seasonal cycles with resurgences during autumn and winter, favoured by cold temperatures. Previous coronavirus outbreaks (SARS-CoV-1 and Middle East Respiratory Syndrome) were also linked to weather[12] (mainly temperature). A climate effect on the wide dissemination of a respiratory disease is a highly intuitive conclusion and SARS-CoV-2 is transmitted mainly through droplets and aerosols. Temperature, humidity and wind were found to impact the spread of this outbreak,[12, 15-19] based on confirmed infections. Notably, biological testing is known to monitor imprecisely this outbreak because 23%–40% of the cases are asymptomatic.[20] Moreover, false-negative reverse transcriptase-polymerase chain reaction results may occur. Therefore, our study focused on more precise, in-hospital deaths, collected in a centralised electronic database.

In many countries spanning multiple latitudes, clear north–south gradients[18, 19] were observed with more deaths further north: France, Spain, Italy, USA (as of 10 December 2020, New York State had more deaths (35 183) than Florida (19 462),[1] despite Florida having a larger population and the highest percentage population in the US >65 years old). Notably, Rome, the largest Italian city with a Mediterranean climate, was proportionally less affected than northern cities,[19] which have a different climate.

Based on our results for continental France, southern and coastal areas seem to be more protected than colder inland areas. Notably, our findings were confirmed by observations made in Spain, where the Madrid region was hit harder than coastal and southern zones. Western Europe (France, UK, Belgium, Netherlands and Germany) has a mainly oceanic climate and the outbreak followed the same course (sudden rise in March, decline in May and resumption in October 2020),[1] despite their different public health-policy approaches. Also, few large cities in East and Southeast Asia (except Wuhan) were COVID-19 pandemic hotspots, despite human-population density being among the highest in the world. That observation can be explained by: (1) aggressive management of the epidemic in cold areas (South Korea, Japan, and China, which implemented the strictest lockdown in the world); (2) other protective behaviours, including traditional cultural distancing; (3) some protective climate effect in warm areas (Hong Kong, Singapore, Taiwan). Of course, the combination of these three factors would achieve the highest protection.

Pertinently, the climate's protective effect alone would not spare a population from the outbreak and, indeed, almost all countries on earth have been impacted. Moreover, the protection afforded by higher temperatures remains to be precisely defined depending on the climate, because the interactions among temperature, humidity, wind and sunlight are complex. Still, Prata *et al*[21] showed that, in Brazil, the climate's effect may exist, even in tropical regions, where the range of temperatures is limited. Inversely, the results of Hallal *et al*'s [22] nationwide antibody-prevalence survey in Brazil showed that the most affected areas were located along the Amazon river, which has the warmest climate. They explained those findings by human density on boats, the major means of transporting people, and excess multifactorial risks among indigenous populations.

Air pollution also was shown to be associated with virus spread in northern Italy,[23] but because pollution is closely related to weather conditions, its independent role remains to be specified.

Public health strategies have been extensively implemented worldwide.[24] It is likely that climate alone is not sufficient to extinguish this outbreak, and public health interventions, aimed at containing and reducing virus circulation, will be needed on a long-term basis. Weather factors and human social behaviours (partly linked to meteorological conditions) seem to contribute to COVID-19 epidemiological dynamics. This multifactorial character could explain why, despite some climate protection, some warm areas in Central and South America are experiencing massive epidemics. Notably, their national strategies implemented only partial social distancing and, even now, persist in opposing it (Brazil,[22] Mexico). Liu *et al*[12] concluded rightly for China: "this epidemic will be faded to a large degree in the coming warmer season with the enforcement of public health interventions in China," which emphasises the absolute need for social distancing and not to rely solely on a weather effect.

Strengths and Limitations

Few countries have simultaneous hospital-data reliability, different climate zones, homogeneous social behaviour during the outbreak (including a uniformly implemented lockdown) and high COVID-19-related mortality. France met all those conditions. However, our study has some limitations. First, the death-toll breakdown per county is available only for in-hospital deaths. Second, the impact of each etiological factor may vary among different countries and climates, therefore, generalisability of our results is mainly valid for temperate countries in the northern hemisphere. Third, the France weather index we used provided a historic collection of weather data, but not winter 2019–2020 conditions. Finally, co-morbidities could not be analysed because of the ecological design of the study but we think that their distribution is relatively homogeneous among French counties.

Conclusion

Our findings suggest that climate is an independent factor influencing COVID-19-linked mortality at the county level in continental France. Human-population density (and therefore social interactions) is an independent factor, whose impact has been widely proven. These factors, along with others (age pyramid, cultural factors, co-morbidities), explain the course of this pandemic throughout the world. The fatality discrepancies among countries and among administrative subdivisions within countries likely follow the same rules worldwide. Our findings also imply that this COVID-19 outbreak will last throughout the coldest periods, but seasonality is complex, as it involves more than climate alone (eg, immune status, virus mutation).

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XK: methodology, writing, manuscript editing. MD: methodology, software, data curation, writing, manuscript editing. All authors have read and approved the submission.

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Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data availability statement: Weather data and epidemiological data are all available free-of-charge from public databases.

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Figure legends

Figure 1 Main climate zones (H1a, H1b, H1c, H2, H3) of continental France counties ("*départements*").

Figure 2 (A) Boxplots of in-hospital mortality rates according to the main climate zones. The internal bold horizontal line is the median; the lower and upper box limits are the 1st and 3rd quartile, respectively; and the T-bars represent range. (B) Multivariate linear-regression analysis (95% confidence intervals (CI); with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.

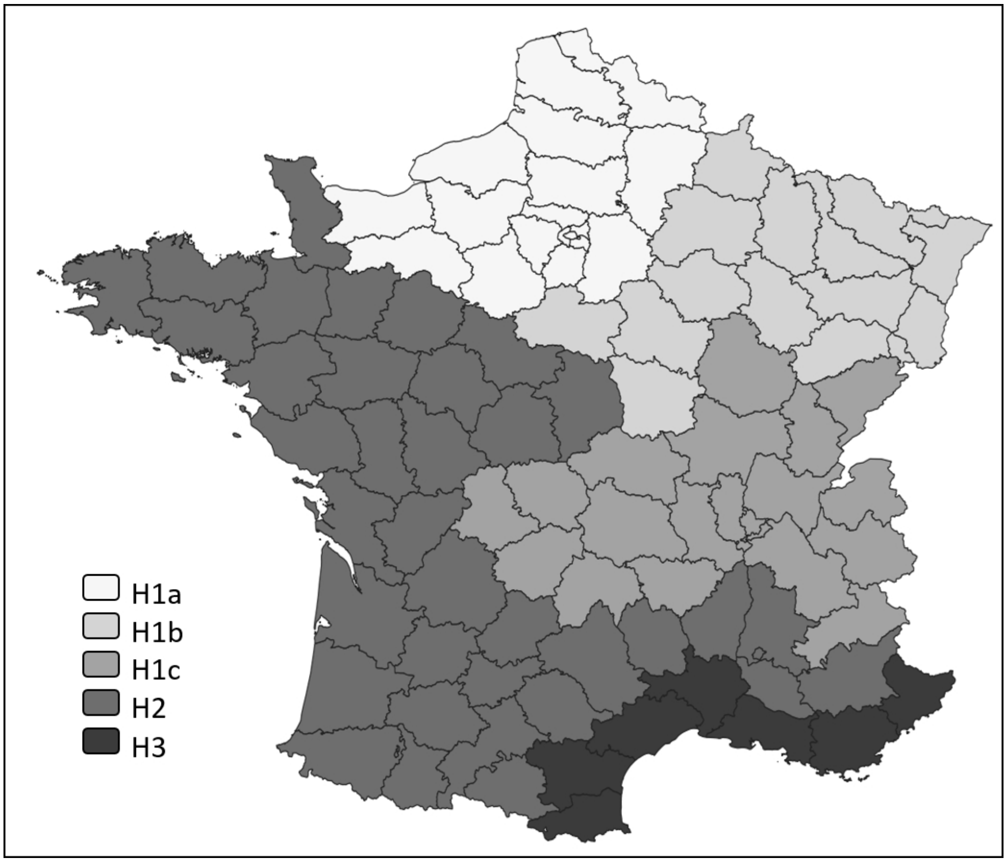

Figure 1. Main Climate Zones (H1a, H1b, H1c, H2, H3) of Continental France Administrative Areas ("Départements").

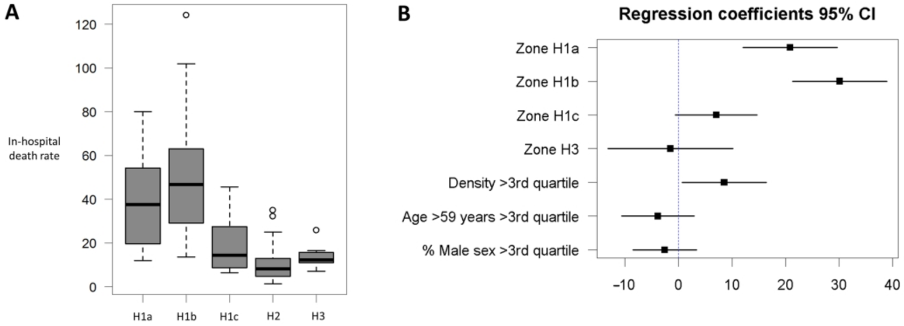

Figure 2. Boxplots of In-Hospital Mortality Rates According to the Main Climate Zones (A). The internal bold horizontal line is the median; the lower and upper box limits are the 1st and 3rd quartile, respectively; and the T-bars represent range. Multivariate linear-regression analysis (B) (95% confidence intervals CI; with H2 serving as the reference). The analysis retained climate zones (H1a, H1b) and population density as independent factors significantly influencing in-hospital mortality.

Supplemental material

Appendix 1 Multivariate multiple-linear regression analysis of initial data

Factor (reference zone H2)	**Regression coefficient [95% CI]**	**p value**
Zone H1a	14.6 [3.8 to 25.4]	0.00962
Zone H1b	37.2 [27.6 to 46.9]	4.39×10^{-11}
Zone H1c	6.0 [–2.7 to 14.9]	0.183
Zone H3	6.9 [–6.9 to 20.8]	0.329
Population density >3rd quartile	0.003 [0.001 to 0.004]	0.000229
Age >59 y >3rd quartile	–0.97 [–1.7 to –0.1]	0.0208
Male sex, % >3rd quartile	5.2 [–2.5 to 13.1]	0.187

Appendix 2 Multivariate multiple-linear regression analysis excluding outliers

Factor (reference zone H2)	**Regression coefficient [95% CI]**	**p value**
Zone H1a	15.2 [6.6 to 23.8]	0.000785
Zone H1b	30.4 [22.1 to 37.9]	7.65×10^{-11}
Zone H1c	6.8 [–0.1 to 13.8]	0.0574
Zone H3	3.4 [–7.5 to 14.4]	0.539
Population density >3rd quartile	0.004 [0.002 to 0.006]	0.00028
Age >59 years >3rd quartile	–0.6 [–1.3 to –0.04]	0.0404
Male sex, % >3rd quartile	0.6 [–5.6 to 6.9]	0.838

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6, 7, 16, 17

		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.