PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Link between COVID-19–related in-hospital mortality in continental France administrative areas and weather: an ecological study
AUTHORS	mejdoubi, mehdi; djennaoui, mehdi; kyndt, xavier

VERSION 1 – REVIEW

REVIEWER	Kennedy Otwombe Perinatal HIV Research Unit Chris Hani Baragwanath Academic Hospital University of the Witwatersrand Johannesburg South Africa
REVIEW RETURNED	19-Sep-2020

GENERAL COMMENTS	SUMMARY REVIEW 1. Title a. Title should reflect that the mortality studied is for those who died in the hospital. Otherwise, the title is misleading as it is since it is possible for people to die from a Covid-19 related complication outside the hospital and in elderly care homes. 2. The abstract does not explicitly state methodology and the statistical method used to derive the results. 3. Strength and limitation a. The first two points state findings of the study. This section should rather mention key strengths and limitations of the study, not the findings. b. An important limitation for this study which is not mentioned is the inability to control for comorbidity in the multivariate analysis. 4. Introduction a. This lacks in-text referencing for the figures cited, dates major events are stated to have occurred and some assertions which may not be common knowledge in the first two paragraphs. b. The time/date events are stated to have occurred are not qualified with the year. E.g. 17 March, 11 May. These should be corrected to reflect the year as well in the introduction and other sections of the manuscript. c. No effort is made to establish with references, the association between Covid-19 and meteorological parameters. Or if studies are lacking, use of past respiratory viral infections and any other study to demonstrate the effect of meteorological parameters on an infectious disease will help set precedence why the team in interested in investigating this particular association. A quick reference here is meningitis in the meningitis belt of Africa which is partially driven by the dry, dusty wind from October to around January and corresponds to the dry season in these locations. d. The indentation for the three paragraphs in the introduction are inconsistent. This is also seen in the methodology, results and

line 26 and 42 of the discussion.

5. Methodology

a. This is well presented and the statistical method used clearly describes what was done and the model fitness tests.

b. The meteorological parameters are well described

c. There is a need, however, to justify why only age>59 years was used and not any other age.

6. Results

a. The second sentence in the first paragraph of the result (line 50) should be accompanied by a measure of association.

b. In page 8 of 22, line 6, the measures association should be included in parenthesis after each significant predictor.

c. In page 8 of 22, line 10 – 20, the sentences are not clear and may be confusing to readers. Which was the first, second and third model? Which model is reported? It is obvious from these sentences a sensitivity analysis was done to compare a model with outliers to the model without outliers. The results of the model which is not reported in the body of the manuscript should be placed as appendix.

d. The model fitness parameters corresponding to the model fitness test stated in the methodology should be mentioned in the results.

7. Discussion

a. There is frequent use of words in parenthesis with several dots possibly indicating many more e.g. (New York, Paris, Madrid, London, …). This is seen in the introduction, throughout the discussion and in the conclusion. This should be avoided and the sentences with this parenthesis should as much as possible, be provided with a reference.

b. Page 9 of 22, line 24 – this sentence and other sentences referring to proven factors which are also predictors of epidemic occurrence should be referenced.

c. If you choose to state the reported death tool in China is subject to question, you may need to offer some explanation for this statement.

d. Page 11 of 22, Line 26 – 36: this sentence asserts valid points with statistics and needs to be referenced.

e. Slight grammatical errors are noted in the discussion and can be corrected by use of grammar and spelling softwares.

8. References

a. References 1, 2, and 3 are not properly written and are missing names of author(s), title, date and date of access. Please use a standardized referencing format for internet sources.

9. Table 3

a. Having a separate column for the statistical test used is not necessary. This can further be described in the methodology or alternatively use a footnote at the bottom of the table to indicate variables the specific statistical test was used for.

b. The mean and median of in-hospital mortality rate reported in this table should be accompanied by the standard deviation and interquartile range.

10. Additional

a. Statement on availability of data used for analysis is missing.

b. Though it is stated patients were not involved, no statement is provided if permission was required to use the meteorological data or if they are freely accessible.

REVIEWER	CARLOS MAGNO CASTELO BRANCO FORTALEZA
	Botucatu School of Medicine, São Paulo State University, Brazil.
REVIEW RETURNED	03-Nov-2020

GENERAL COMMENTS	This ecologic study addressed demographic and climatic patterns of French administrative areas as predictors of in-hospital deaths from COVID-19. It is generally well-written and clear in regard to introduction, objectives and methods. The data sources are cited in the study, and include hospital deaths database and climatic classifications based on coldness during winter. The most important result is presented in Table 3, which depicts a multivariable linear regression model including what the authors classify as "typical administrative areas" (i.e., excluding outliers such as Paris and those areas presenting very early introduction of COVID-19). There are some aspect which deserve further clarification.
	1. First, it is not clear if deaths were assigned to the areas harboring the hospitals or to the areas where the deceased persons lived.
	2. Also, since the authors themselves report that deaths not occurring in the hospitals could not be assessed, the availability of hospital beds (measured, for instance, by the number of hospital beds per 100,000 inhabitants) is a relevant confounder that must be included in the multivariable model.
	3. The discussion is extensive, and from our perspective too much relevance is placed on the role of climate on the epidemiology of COVID-19. To give an example, the authors cite Prata's article to suggest that even in Brazil the climate influenced transmission of SARS-Cov-2. However, Prata's data are objetable, because they only measure the incidence from February 27th to April 1st , when COVID-19 mostly affected cities around São Paulo and Rio de Janeiro, which harbor the major international airports in Brazil. In the following months, the most affected area was the Amazon and Northeastern Coastal areas, indeed the warmest climates in that country (see Hallal PC et al. SARS-CoV-2 antibody prevalence in Brazil: results from two successive nationwide serological household surveys. Lancet Glob Health. 2020 Nov;8(11):e1390-e1398; article uploaded alongside this review). Therefore, Prata's data are in the best scenario outdated, in the worst scenario simply wrong, and cannot be cited to reinforce the authors opinion on climate impact on COVID-19 deaths. Overlooking Hallal's impressive countrywide prevalence surveys is an example of selecting and citing only studies that agree with the authors pre-conceived opinions.
	4. In a similar sense, the authors cite outbreaks in climatized facilities ("The weather effect may also be supported by the massive infections observed in climatized facilities, in meat processing facilities (in USA, France, and Germany) or in boats…") as findings reinforcing their opinion on the impact of coldness on SARS-Cov-2 transmission. This is inappropriate since those outbreak settings present several other aspects (such as overcrowding) that can explain increased transmission.
	5. Even though the authors repeatedly make statements that "… the climate's protective effect alone would not spare a population…", "the absolute need for social-distancing and not to rely solely on a weather effect", they take for granted their climate hypothesis as far as stating that Latin American countries experience massive COVID-19 outbreaks "despite some climate protection". Well, where is the evidence for "some climate protection" (since we have seen that Prata's study is misleading)?
	In conclusion, this study is of interest, but it requires: (i) stating if deaths are assigned to hospital or residence of the deceased; (ii)

	adjusting model to the density of hospital beds; (iii) rewriting the discussion and toning down the climate-based conclusion.

VERSION 1 – AUTHOR RESPONSE

2) Reviewer: 1
Reviewer Name: Kennedy Otwombe
Institution and Country: Perinatal HIV Research Unit
Chris Hani Baragwanath Academic Hospital
University of the Witwatersrand
Johannesburg, South Africa
Please state any competing interests or state 'None declared': None

Comments to the Author
See attachment: SUMMARY REVIEW 19Sep2020.docx

Title

a. Title should reflect that the mortality studied is for those who died in the hospital.

Otherwise, the title is misleading as it is since it is possible for people to die from a

Covid-19 related complication outside the hospital and in elderly care homes.

As requested, the title has been modified to: Covid-19–related in-hospital mortality in continental France administrative areas is linked to weather: an ecological study.

2. The abstract does not explicitly state methodology and the statistical method used to derive

the results.

The methodology is now given in the Abstract.

3. Strength and limitation

a. The first two points state findings of the study. This section should rather mention key strengths and limitations of the study, not the findings.

The strengths and limitations have been revised.

b. An important limitation for this study which is not mentioned is the inability to control for comorbidity in the multivariate analysis.

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That is indeed an important point. It has now been added (page 15, line 9) and specified that co-morbidities could not be controlled because of the ecological design of the study.

4. Introduction

a. This lacks in-text referencing for the figures cited, dates major events are stated to have occurred and some assertions which may not be common knowledge in the first two paragraphs.

We added references [1, 2] to support the figures, dates and major events.

b. The time/date events are stated to have occurred are not qualified with the year. E.g. 17 March, 11 May. These should be corrected to reflect the year as well in the introduction and other sections of the manuscript.

2020 has been added.

c. No effort is made to establish with references, the association between Covid-19 and meteorological parameters.

We added references [18, 19, 22].

Or if studies are lacking, use of past respiratory viral infections and any other study to demonstrate the effect of meteorological parameters on an infectious disease will help set precedence why the team in interested in investigating this particular association. A quick reference here is meningitis in the meningitis belt of Africa which is partially driven by the dry, dusty wind from October to around January and corresponds to the dry season in these locations.

d. The indentation for the three paragraphs in the introduction are inconsistent. This is also seen in the methodology, results and line 26 and 42 of the discussion.

We corrected these typographical inconsistencies.

5. Methodology

a. This is well presented and the statistical method used clearly describes what was done

and the model fitness tests.

b. The meteorological parameters are well described

c. There is a need, however, to justify why only age>59 years was used and not any

other age.

This is a well-taken point. Surveillance data for the epidemic in France from *Santé Publique France* indicates that 93% of the COVID-19 patients that died were aged ≥65 years [1]. However, the demographic data by age group to which we had access via the French Institute for Statistics and Epidemiology INSEE database [2] did not allow us to choose an age threshold at 65 years (age-group options: [0–19], [20–39], [40–59], [60–74], >74); we therefore considered the age threshold for the risk of death at >59 years. As now specified on page 5, lines 19–20.

[1] https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/documents/bulletin-national/covid-19-point-epidemiologique-du-26-novembre-2020.

[2] https://www.insee.fr/fr/statistiques/1893198.

6. Results

a. The second sentence in the first paragraph of the result (line 50) should be accompanied by a measure of association.

We apologize for this oversight. Means (standard deviation) (page 7, line 10; reported in table 2) and correlation coefficients (page 8, line 3; reported in table 3) are now specified.

b. In page 8 of 22, line 6, the measures association should be included in parenthesis after each significant predictor.

Regression coefficients and their corresponding p-values have been added (pages 9, lines 5–11); they are reported in supplemental appendixes 1 and 2. We did not repeat these values in the text, as stipulated in the instructions for authors.

c. In page 8 of 22, line 10 – 20, the sentences are not clear and may be confusing to readers. Which was the first, second and third model? Which model is reported? It is obvious from these sentences a sensitivity analysis was done to compare a model with outliers to the model without outliers. The

results of the model which is not reported in the body of the manuscript should be placed as appendix.

We clarified the three multivariate models (page 6, lines 11, 16 and 20) used in the manuscript and added supplemental appendixes 1 and 2, which report the successive stages of the statistical analysis (mention of/showing intermediate results).

d. The model fitness parameters corresponding to the model fitness test stated in the

methodology should be mentioned in the results.

Residual analyses using initial data and excluding outliers, respectively, are given below for your information.

Residual analyses of the multiple-linear regression model using initial data.
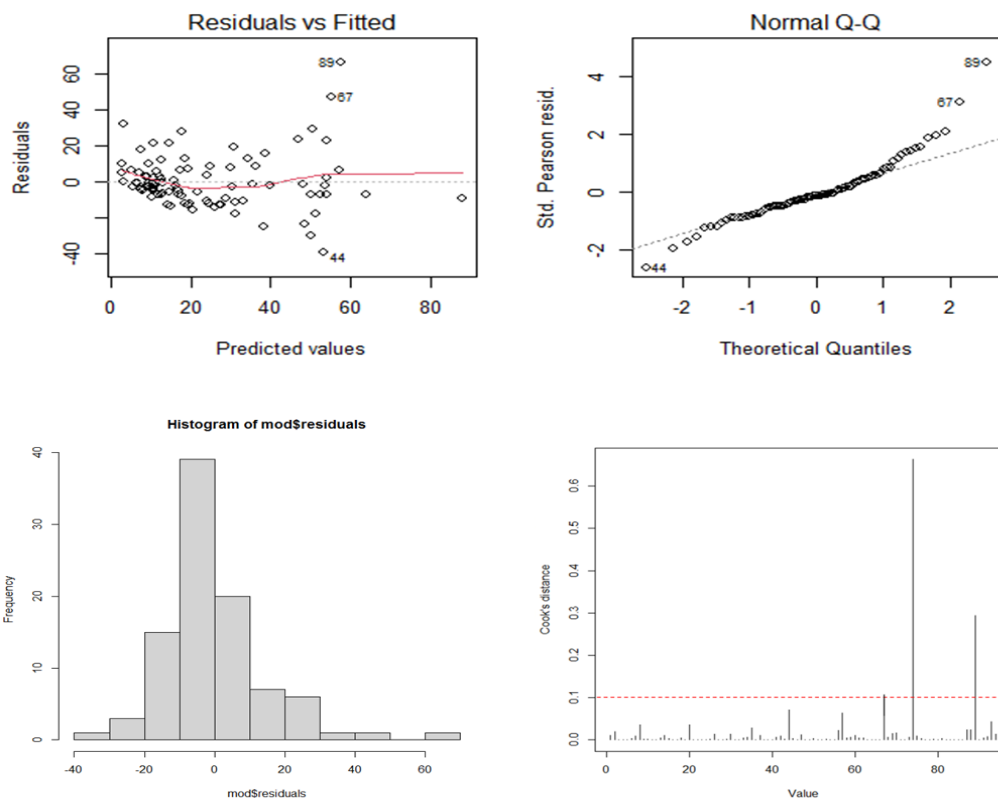
Residual analyses of the multiple-linear regression model excluding outliers
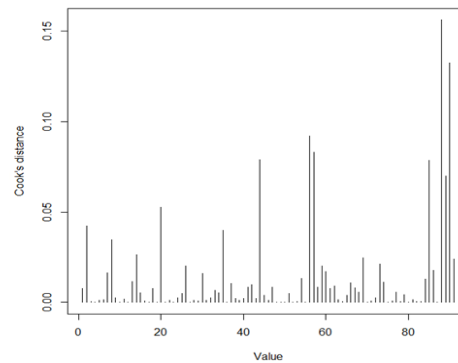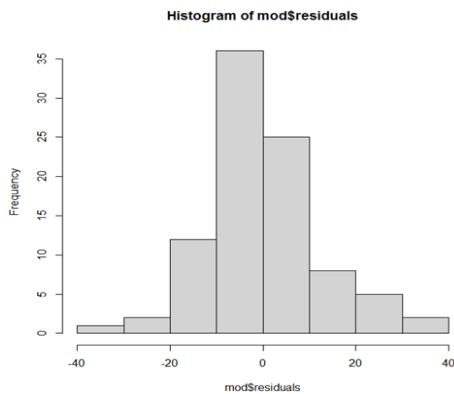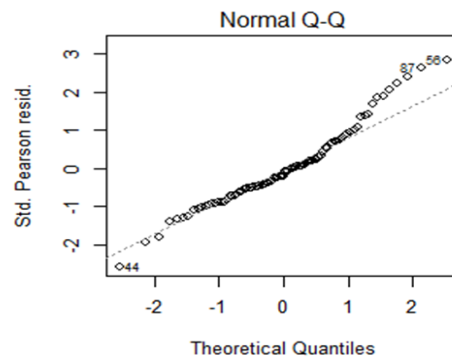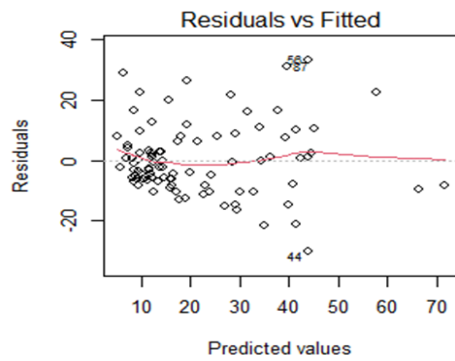
7

Residuals vs Fitted

Normal Q-Q

Histogram of mod$residuals

7. Discussion

a. There is frequent use of words in parenthesis with several dots possibly indicating many more e.g. (New York, Paris, Madrid, London, ...). This is seen in the introduction, throughout the discussion and in the conclusion. This should be avoided and the sentences with this parenthesis should as much as possible, be provided with a reference.

The requested changes have been made.

b. Page 9 of 22, line 24 – this sentence and other sentences referring to proven factors which are also predictors of epidemic occurrence should be referenced.

The corresponding references [6, 7, 8, 9, 13] have been added.

c. If you choose to state the reported death tool in China is subject to question, you may need to offer some explanation for this statement.

We deleted this statement (page 10, line 10–11) as it is a minor point.

d. Page 11 of 22, Line 26 – 36: this sentence asserts valid points with statistics and needs to be referenced.

We added reference [19].

e. Slight grammatical errors are noted in the discussion and can be corrected by use of grammar and spelling softwares.

We apologise for those errors. Purely grammatical and spelling corrections are not indicated in the revised text.

8. References

a. References 1, 2, and 3 are not properly written and are missing names of author(s),

title, date and date of access. Please use a standardized referencing format for internet

sources.

We corrected the references accordingly.

9. Table 3

a. Having a separate column for the statistical test used is not necessary. This can further be described in the methodology or alternatively use a footnote at the bottom of the table to indicate variables the specific statistical test was used for.

This presentation is indeed less cumbersome; thank you for suggesting it. The tests are indicated in the footnotes.

b. The mean and median of in-hospital mortality rate reported in this table should be accompanied by the standard deviation and interquartile range.

We completed table 3, adding the standard deviation and interquartile range.

10. Additional

a. Statement on availability of data used for analysis is missing.

Weather data and epidemiological data are all available free-of-charge from the public databases indicated in the text.

b. Though it is stated patients were not involved, no statement is provided if permission

was required to use the meteorological data or if they are freely accessible.

Concerning patients, we added: Patients and/or the public were not involved in

the design, or conduct, or reporting, or dissemination plans of this research. Free access to these databases is stated in response to a.

3) Reviewer: 2
Reviewer Name: CARLOS MAGNO CASTELO BRANCO FORTALEZA
Institution and Country: Botucatu School of Medicine, São Paulo State University, Brazil.
Please state any competing interests or state 'None declared': None declared

Comments to the Author
This ecologic study addressed demographic and climatic patterns of French administrative areas as predictors of in-hospital deaths from COVID-19. It is generally well-written and clear in regard to introduction, objectives and methods. The data sources are cited in the study, and include hospital deaths database and climatic classifications based on coldness during winter. The most important result is presented in Table 3, which depicts a multivariable linear regression model including what the authors classify as "typical administrative areas" (i.e., excluding outliers such as Paris and those areas presenting very early introduction of COVID-19). There are some aspect which deserve further clarification.

1.   First, it is not clear if deaths were assigned to the areas harboring the hospitals or to the areas where the deceased persons lived.

We specified (page 5, lines 14–15) that the deaths were assigned to the areas where the deceased persons lived.

2.   Also, since the authors themselves report that deaths not occurring in the hospitals could not be assessed, the availability of hospital beds (measured, for instance, by the number of hospital beds per 100,000 inhabitants) is a relevant confounder that must be included in the multivariable model.

In France, access to healthcare is free and, during this outbreak, there was no shortage of available conventional or ICU hospital beds. Also, the number of hospital beds per French county (administrative *département*) per 100 000 inhabitants was homogeneously distributed, as evidenced by the low dispersion of the distribution; the distribution is even more restricted if we consider only the

91 counties on which the final statistical model is based. As a result, the role of this parameter as a confounding factor is weaker than other factors considered in our study.
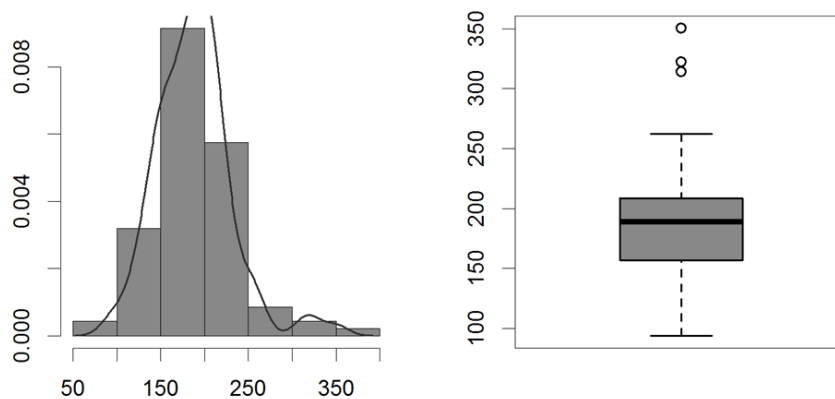
Hospital beds in French counties per 100 000 inhabitants

	Initial database	Database excluding outliers
Count	94	91
Mean	187.7	184.4
SD	43.0	37.8
95% CI	[178.9–196.5]	[176.5–192.3]
Minimum	94.0	94.0
Quartile 1	157.4	155.2
Median	189.1	187.2
Quartile 3	208.2	205.7
Maximum	350.3	322.1

*Data from the annual statistics of French health facility SAE database https://www.sae-diffusion.sante.gouv.fr/sae-diffusion/recherche.htm
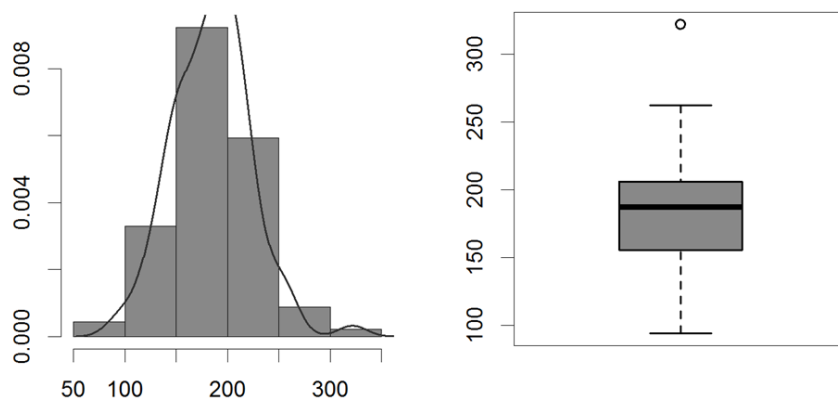
Hospital beds in French counties per 100 000 inhabitants: initial database

The box plot on the right reports: internal bold horizontal line is the median; the lower and upper box limits are the first and third quartiles, respectively; and the T-bars represent range.

Hospital beds in French counties per 100 000 inhabitants: database excluding outliers

The box plot on the right reports: internal bold horizontal line is the median; the lower and upper box limits are the first and third quartiles, respectively; and the T-bars represent range.

3.   The discussion is extensive, and from our perspective too much relevance is placed on the role of climate on the epidemiology of COVID-19. To give an example, the authors cite Prata's article to suggest that even in Brazil the climate influenced transmission of SARS-Cov-2. However, Prata's data are objetable, because they only measure the incidence from February 27th to April 1st , when COVID-19 mostly affected cities around São Paulo and Rio de Janeiro, which harbor the major international airports in Brazil. In the following months, the most affected area was the Amazon and Northeastern Coastal areas, indeed the warmest climates in that country (see Hallal PC et al. SARS-CoV-2 antibody prevalence in Brazil: results from two successive nationwide serological household surveys. Lancet Glob Health. 2020 Nov;8(11):e1390-e1398; article uploaded alongside this review). Therefore, Prata's data are in the best scenario outdated, in the worst scenario simply wrong, and cannot be cited to reinforce the authors opinion on climate impact on COVID-19 deaths. Overlooking Hallal's impressive countrywide prevalence surveys is an example of selecting and citing only studies that agree with the authors pre-conceived opinions.

Thank you for this excellent reference, now cited as [22] in the modified Discussion (page 13–14, starting line 22–1).

4.   In a similar sense, the authors cite outbreaks in climatized facilities ("The weather effect may also be supported by the massive infections observed in climatized facilities, in meat processing facilities (in USA, France, and Germany) or in boats…") as findings reinforcing their opinion on the impact of coldness on SARS-Cov-2 transmission. This is inappropriate since those outbreak settings present several other aspects (such as overcrowding) that can explain increased transmission.

We agree and fully recognize the impact of overcrowding and, therefore, deleted this sentence and the corresponding reference.

5.   Even though the authors repeatedly make statements that "… the climate's protective effect alone would not spare a population…", "the absolute need for social-distancing and not to rely solely on a weather effect", they take for granted their climate hypothesis as far as stating that Latin American countries experience massive COVID-19 outbreaks "despite some climate protection". Well, where is the evidence for "some climate protection" (since we have seen that Prata's study is misleading)?

We modified the Discussion accordingly.

In conclusion, this study is of interest, but it requires:

(i) stating if deaths are assigned to hospital or residence of the deceased;

(ii) adjusting model to the density of hospital beds;

(iii) rewriting the discussion and toning down the climate-based conclusion.

VERSION 2 – REVIEW

REVIEWER	CARLOS MAGNO CASTELO BRANCO FORTALEZA Botucatu School of Medicine, São Paulo State University, Brazil
REVIEW RETURNED	03-Feb-2021

GENERAL COMMENTS	The authors responded to the reviewers' comments and requests, and the revised manuscript is improved, especially in regard to assuming the difficulties in generalization of their findings. Other study limitations were discussed, so that the inferences are now appropriately presented to readers.