Author’s response to reviews

Title: Acclimatization across Space and Time in the Effects of Temperature on Mortality

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Author’s response to reviews: see over
Dear Editor in Chief:

I am pleased to submit the revised copy of our original article entitled “Acclimatization across Space and Time in the Effects of Temperature on Mortality: A Time-series Analysis” by Mihye Lee, Francesco Nordio, Antonella Zanobetti, Patrick Kinney, Robert Vautard, and Joel Schwartz for consideration for publication in the Environmental Health.

After we had received referees’ report, we modified our manuscript accordingly. Please find the following bullet by bullet point answers to them starting with the next page.

We also changed our manuscript according to your journal style such as title form or the structure of manuscript.

Please let me know if you need more amendment although we tried our best to fit your journal style and to deal with referee’s points.

Thank you for your consideration.

Sincerely,
Mihye Lee
Doctoral Student, Department of Environmental Health
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Referee 1.

Reviewer's report:

Major Compulsory Revisions

1. The authors need an expansion of their methodology section on data variables.
   a. On Line 88, the authors need to list the actual weather variables applied. They also need to explain how they handled cities with multiple weather monitors and the impact of missing weather data (if any existed). If data was missing, how did this further impact the monthly estimates of mortality change for a given city?
   Reinforced the data section.

   b. How did the authors decide upon the cities to initially examine in their model? Was there a population cutoff for inclusion? The authors need to include a sentence clarifying the definition of a city (e.g. the city proper or did it include surrounding counties?). On Line 95, the author should include the actual denominator of total possible cities examined before selecting their final 148.
   Reflected in line 87-89.
   And since it is the daily count of death as an outcome, we only needed to calculate the mean of those counts (no need for the denominator)

   c. Where did the authors get their data for visibility from and how is this estimated (a numeric scale, categorical, etc.)? This information should be included either in the manuscript or a supplement.
   Added in line 93-94

2. The inclusion of Spokane, Salt Lake City, and Albuquerque (traditionally low humidity and high altitude western cities) into Cluster 1 is very curious, considering that the rest of the cluster is dominated by eastern U.S. fairly high humidity and very seasonal cities. With the details on the clustering methodology currently unpublished, the authors need to explain or justify this discrepancy.
   Reinforced the line 109-115

3. The authors need to justify why they presented in Figures the monthly results for heat effects by Cluster 1 and cold effects for Cluster 2, and not any other clusters, especially since they state that effects for cold were greatest in Cluster 8.
   Stated in line 167-169 and 187-189

4. In presenting their results, the authors do not reference any statistical significance of their estimates. It would be valuable to the readers to know if changes in mortality trend by cluster were significantly different from one another. If statistical differences are observed, this might support the author’s initial hypothesis about the impact of geographic location on mortality.
   We actually presented the 95% confidence intervals in table 2. Also added line 183-186

5. It is my opinion that that Figure 7 and Table 4, representing the sensitivity tests for visibility, are not very useful and don’t add much to your overall conclusions.
Without having the estimates from both models side by side for comparison, it is difficult to immediately observe the impact of air pollutants on the effect estimates. Additionally, since air pollution did not have a major effect on the model (and confirmed by cited literature), perhaps these tables would be better suited for a Supplement?

If the authors do insist on keeping these tables, I would suggest reporting differences in monthly effect estimates for models with and without visibility, rather than the raw results.

Our intention is to prove the robustness of our model. As I understand, the aim of sensitivity analysis to evaluate how the model is robust to other factors. In our case, the competing confounder of temperature effect on mortality is air pollution. Therefore, the fact that the result from the sensitivity analysis didn't change is critical point in proving that there is actual temperature effects on mortality even after controlling for the possible confounding of visibility. Our main model doesn't include the visibility in table 2 and we presented it in table 4, where readers can compare the numbers.

**Minor Essential Revisions**

1. Remove empty parentheses on Page 3, Line 52 of the Abstract
   - Removed. Thank you.

2. Did the authors mean ‘dose-response relationships’ on Line 65?
   - Yes. Therefore, I changed the ‘relations’ to the ‘relationships’.

3. The paragraph starting on Line 194 references a Figure not in the manuscript and a Table describing a different sensitivity test. This needs to be revised.
   - Changed

4. On Line 228, the word ‘Figure’ should be capitalized.
   - Capitalized

5. In Line 246, the authors mention a hypothesis that strong heat resistance in the desert Cluster may be due to low relative humidity. However, the initial model controlled for RH, so couldn’t this be confirmed statistically?
   - The model controlling for RH is actually the first stage modeling for each day within city. And our final model, the second stage model is performed by cluster, where still variations in climate exist. Therefore, the regional characteristics can be suggested in explaining the regional differences in final estimates.

6. In Figure Legend 1, change ‘cluster is in the parenthesis’ to ‘cluster is in parentheses.’
   - Reflected. Thank you

**Discretionary Revisions**
1. On Line 102, I'm not sure if the authors can cite an unpublished source.
When we initially submitted the original manuscript, we expected that unpublished manuscript would be published. Now, we resolved it by reinforcing the method section explaining the method in more detail.

2. In Table 1, it would be informative for the authors to add an additional column describing the basic environment of each cluster (e.g. Cluster 8 – Subtropical warm humid, Cluster 2 – Northern cold winters, etc.)
We thought the same way, but since our clustering is not based on climatology but purely on statistics (cluster analysis), we decided to minimize label the clusters implying the climate specification.

3. In Figures 5 and 6, the two legends for Cluster ID and Temperature percentile were found to be confusing. For this reviewer, it would be logical to have a single legend and add the percentile value next to the Cluster ID in parentheses.
Our intention was ordering by two definitions. The first section of legends is by cluster ID and the second section is ordered by the highest percentile and the order of graph lines from the top to the bottom. If we put the legend together, it would be jumbled.

4. As a reader, I found the Figure captions to read very interpretively which should be reserved for the text and/or left up to the reader to conclude. I would recommend a simpler caption that presents the Figure such as, “Cluster heat effects in July and the associated temperature percentile at 30 degrees Celsius.” However, I leave it to the author’s discretion if they want to make this change.
Our intention was to guide readers to see quickly what we like to present.

5. For visual purposes, projecting the map in Figure 1 into Albers Equal Area would improve the appearance by reducing stretching in the northern states and shrinking the amount of white space.
Since our intention is just displaying the distribution of cities and corresponding cluster, we believe the figure 1 fully serves.

Thank you for your valuable inputs and comments!!
Referee 2.

Major Compulsory Revisions

Abstract
43: I suggest something like this: “few have examined whether this association varies depending on the exposure month”, instead of “few have examined the timing of exposure in separate months”.
Ł I appreciate your suggestion and reflected it the new wording.

45: “and we investigated heterogeneity among regions” instead of “and compare it to regional differences”.
Ł Reflected it the new wording.

52: there is a “()”.
Ł Deleted. Thank you.

Introduction
60-62: Add appropriate references which support this statement.
Ł Added

79-82: Simplify the explanation which is a bit long and not easy to understand. For example: “Results from cities belonging to the same cluster were combined to obtain a more robust estimate of how temperature effect varies by month, and the resulting exposure-response curves were compared among clusters”.
Ł Reflected. Thank you for your suggestion.

Data
- In assigning the “closest” station to each city, have the authors taken into account possible differences in altitude between the city and the selected monitor? They could add a comment on this.
Ł Since we didn’t have the altitude of the city and the monitor, we couldn’t consider it. However, the most of the monitoring stations is located in the airport, the altitude didn’t play a role in our analysis. We mentioned this in line 100-101.

Statistical analysis
99-102: The clustering procedure should be better explained in the text and appropriated published papers should be cited together with the software used for the analysis.
Ł Reinforced the methodology in line 110-116

105-108: If I understand well, separated time-series analyses by city and month were performed. If so, in order to simplify the model and avoid correlation between TMP terms, one could estimate a model with a lag 0 or a lag 0-1 effect for the summer-spring months and a model with a lag 0-5 effect for the autumn-winter months. I think that a sensitivity analysis should be done because it is not trivial motivating that the cold effect was measured after excluding the effect of the current exposure (lag 0).
Ł We actually dealt with that point in the line 113: “To check the collinearity between the lag 0 lag 1-5, the correlation coefficients were calculated” and the line 177:” For
reference, correlation between lag 0 and lag 1-5 was the average of 0.53 where those correlation were weak.

108-109: The authors write: “For consistency, temperatures were centered to 18 °C at which the lowest mortality was when the centering was not applied”. First, I think it is unlikely that 18°C correspond to the lowest mortality in each city enrolled in the analysis. Second, it is not completely clear to me why the centering is needed. Probably it is just a simple way to directly obtain results in terms of percent increase in mortality associated to a temperature variation from 18°C to x °. The authors should clarify this point.

First, it is observed in the data in our hand, where 18 °C and it is the pleasant temperature.
Second, the reason we applied centering is to make the intercept is more plausible, therefore make our interpretation on results (% increase) sensible. If we don't apply the centering, the reference temperature will be 0 °C which is not an appropriate reference temperature especially for summer.

- Moreover, it is not clear (if we consider rows 194-196) whether centering around 18 °C was used only in a sensitivity analysis.
- That is the outdated phase after we changed our model. I am sorry. We used centering around 18 °C in all models. We also erased rows 194-196.

- Finally, did the authors center both temp0 and temp15?
- Yes, both of them.

110-111: The authors write: “The model controlled for linear trend over the 34 years”. If I understand well, Time is the linear term which they refer to. Is this equal to 1 for the first year, 2 for the second and so on? I think a more clear explanation is needed. I suggest to call this variable Y (or Year) instead of Time.

Time is a daily term to control for the trend. So I added in line 112-113, and 118.

113: RHij and DOWij should be replaced by RHijt and DOWit, respectively. Moreover, the regression coefficients should be included in the formula:
- Reflected. Thank you.
As an alternative, for simplicity you could remove from the formula the subscripts for month and city:
- To emphasize that we ran the model separately for each month and city, which is the essential part of our analyses, I would leave the subscripts at they are.

114-117: This statement should be revised according to the previous suggestions. Particular attention should be reserved to the penalized spline definition (if I understand well it indicates a penalized spline function, defined by using a cubic spline basis with 10 initial knots placed in the quantiles of the temperature distribution), the meaning of λ (which is the EXPECTED number of daily deaths) and the definition of DOW(t), which is an indicator of the day of week.
- By definition of Poisson regression, the meaning of λ is the expected mortality rate, not the number of deaths without offset. I added the ‘expected’ for λ and the ‘indicator variable’ for dow.

118: I suggest the following change: “We assumed a quasi-Poisson distribution for λ to account for any over-dispersion”. 
Reflected. Thank you.

In performing the random effect meta-analysis for each temperature, did the authors consider the correlation among points belonging to the same exposure-response curve (i.e. to the exposure-response curve of the same city)? Could the omission of this information have an impact on the final meta-analytic curve? Did the authors evaluate the heterogeneity among cities within each cluster? And the uncertainty around the final curves?

The aim of the clustering is to maximize the homogeneity within each cluster and maximize the heterogeneity between clusters. The uncertainty was calculated by providing the 95% confidence intervals.

Usually the effect of humidity on mortality is quadratic. Was this point explored? Yes, but it didn’t change the results.

This explanation is not clear. Deleted, not intended to put

**Results**

- Table 1: Reporting temperature by season (winter-autumn and spring-summer) would be more appropriate. Add also the descriptive statistics for humidity.

- It is not clear what Figures 2, 4, 5, 6 show. I suppose that these curves derive from the meta-smoothing, but this is not clear from the text.

- Line 169-177 explained Figure 2. Line 189-196 explained Figure 4. Line 197-203 explained Figure 5. Line 204-209 explained Figure 6.

The authors write: "Figure 2 shows the monthly effects of heat on mortality (i.e. lag0 temperature) in the first cluster. Each curve represents a month from April to September and shows the percent increase in mortality versus temperature compared to the expected deaths in that month". Maybe it would be better to write: “…compared to the expected level of daily deaths in that month if we assume that temperature is equal to ….”. Changed the sentence for clarification.

This is not clear. Deleted to avoid confusion.

- I suggest that the authors include in the paper a figure showing the percent variation by month for the effect of cold.

- Figure 4 shows the percent variation by month for the effect of cold.

1°C instead of -10 °C?
No, -10 °C is correct. Please refer to the x-axis in Figure 4.

- Table 3 is not cited in the text. Moreover, the presence of N/A in this table should be motivated.

- We took out Table 3.

- Regarding the cold effect, did the authors inspect the spline for the current (lag 0)
exposure?
Ł Since the cold effect shows the lingered lag, we investigated lag 1-5 for cold effect. Lag 0 was used to investigate the heat effect considering the heat effect is more immediate.

Discussion
212-213: The results do not indicate that acclimatization occurs over longer term across cluster, but simply that there is a difference among clusters which is consistent with the idea that the response depends on a “general degree of acclimatization”.
Ł Deleted

216-217: Clarify the following comment: “that does not explain phenomena such as the constant pattern of monthly effects as shown in Figure 2”.
Ł Modified in rows 228-231.

219-220: The depletion can be observed during a period which is longer than one week. So that it is really difficult to disentangle harvesting effect and acclimatization effect.
Ł Although we are with it, harvesting effect can’t explain everything. Therefore, as an explanation, we suggested both, the harvesting effect and adaptation. Therefore, in discussion, we tried put a caution in dealing with it by putting “usually”, “may not be explainable solely “, “would”, “another”, etc. We also modified and added line 231-237.

Minor Essential Revisions
Check for missing spaces between words and for the use of “the”.
Ł Checked

When the authors cite a result which is not shown (for example at row 161), they should specify in the text that the results are not shown.
Ł Added ‘results not shown’ phrase.

Thank you for your valuable inputs and comments.