Author’s response to reviews

Title: Extreme ambient temperatures and cardiorespiratory emergency room visits: assessing risk by comorbid health conditions in a time series study

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Author’s response to reviews: see over
January 20th, 2014

Dear Dr. Ebi,

Thank you for considering a revised version of our manuscript “Extreme ambient temperatures and cardiorespiratory emergency room visits: assessing risk by comorbid health conditions in a time series study”. We have addressed all of the reviewers’ concerns. A revised version of the manuscript in a Word document with “Track changes” mode is included in order to facilitate the identification of changes made in the text. We have copied and pasted all reviewers’ comments below and a response for each one has been provided below the comments. We are also including two figures to put in appendix. We believe that these figures will address some of the reviewer’s comments. As you will see in the revised version, we have made every attempt to incorporate the suggestions as thoroughly as possible.

We thank the two reviewers as their comments have been highly constructive and very useful.

We hope that all these changes fulfill the requirements to make the manuscript acceptable for publication in *Environmental Health*.

Looking forward to hearing from you soon.

Yours sincerely,

Eric Lavigne on behalf of the authors.
1st reviewer comments (Yuming Guo)

Comment # 1:

1. Abstract
Methods: “estimated using distributed lag non-linear Poisson regression models” should be “using a Poisson regression model with distributed lag non-linear model”.

Response:

We agree with the reviewer’s comment and we have made the following modification (underlined text) in the abstract of the paper: “Relative risks (RRs) and their corresponding 95% confidence intervals (CIs) were estimated using a Poisson regression model with distributed lag non-linear model, and were adjusted for the confounding influence of seasonality, relative humidity, day-of-the-week, outdoor air pollutants and daily influenza ER visits.”

Comment # 2:

The introduction seems to be short. The authors are better to describe what have done in Canada, and summarise if previous studies have done similar study worldwide.

Response:

We have added the following paragraph in the introduction: “Previous studies in Canada have shown health impacts in the days following exposure to cold and hot temperatures (8-11). Although no previous study investigated comorbidity factors that increase susceptibility to temperature extremes in Canada, previous studies in other parts of the world have reported that pre-existing medical conditions such as diabetes, respiratory diseases and cardiovascular diseases may increase the risk of death during hot and cold days (6,7,12,13). However, most research to date has investigated susceptibility to temperature extremes on mortality, with less attention in identifying vulnerability factors to temperature on morbidity outcomes.”

Comment # 3:

It is better to plot the lag structure, so the readers are easy to understand why there are significant effects at short lags but not long lags for hot effect. Maybe put the figures to appendix.

Response:
We have provided two figures showing the three dimensional relationship between temperature and emergency room visits for cardiovascular diseases and respiratory diseases for each temperature values along lag days. We believe that these additional figures are addressing the reviewer’s comment. We have also added the following text at the beginning of the results section in order to briefly explain these graphs: “In appendix, Figures 1 and 2 are showing three-dimensional graphs of the relative risks of emergency department visits for cardiovascular and respiratory diseases by temperature (°C) and lag days. These graphs show that the effects of hot temperatures on emergency room admissions are generally seen within a few days of the hot day while the effects of cold temperatures are more delayed in time.”

Comment # 4:

As some subgroups have very limited counts, the reviewer suggest use case-only study to examine which subgroup is at greater risk, using multi-logistic regression with distributed lag non-linear model. This part could be put to the appendix, but it is very useful to assess which group is more sensitive to the effects of extreme temperatures.

Response:

We understand the importance of the reviewer’s comment in addressing which subgroups are more susceptible to temperature extremes. In order to address this issue, we calculated the statistical significance of effect modification by comorbid health conditions using the relative effect modification (REM) index which has been previously used in the context of a time series study using Poisson regression models in evaluating susceptibility by comorbid health conditions (Stafoggia et al. 2006). The relative effect modification (REM) index is the ratio between the relative risk (RR) when comorbidity is present and when the comorbid health condition is absent (reference category). The REM can be interpreted as the relative increase in risk for an emergency room visit for persons with a comorbid health condition compared to those without the health condition. It’s a similar interpretation as the one that would be used with the case-only analysis.

We have added the following text in the methods section (statistical analysis) in order to explain the use of this approach: “We investigated effect modification by comorbid health conditions by calculating the relative effect modification (REM) index which is the ratio between the relative risk (RR) when comorbidity is present and when the comorbid health condition is absent (reference category) (23). The REM can be interpreted as the relative increase in risk for an emergency room visit for persons with a comorbid health condition compared to those without the health condition. The statistical significance of the REM was tested with the calculation of its 95% confidence interval.

We have also ensured throughout the text, the abstract as well as in the tables that the interpretation of the results now focus on the REM by providing the additional risk a person would have if the comorbidity condition is present compared to those who don’t have the underlying medical condition.
Comment # 5:

As table 1 showing, there are some missing values for O3 and CO. The reviewer suggests interpolate the missing values by the mean of previous and following days’ concentration.

Response:

As suggested by the reviewer, we have interpolated the missing values for O3 and CO by the mean of previous and following days’ concentration. This approach did not change the final results. We have added the following text in the methods section to clarify the use of this approach: “A minimal amount of missing values was observed for O3 and CO. We interpolated the missing values for these pollutants by using the mean of previous and the following days’ concentration.”

Comment # 6:

Table 2: 3109 should be 3,109.

Response:

We have made the change.

Comment # 7:

Table 3 and table 4 can be structured into one table.
Table 5 and table 6 can be structured into one table.

Response:

We have merged Tables 3 and 4 together (now called Table 3) and Tables 5 and 6 together (now called Table 4).

Comment # 8:

Citation 22 and 14 are the same paper. Please change 14 to “The Impact of Temperature on Mortality in Tianjin, China: A Case-Crossover Design with a Distributed Lag Nonlinear Model”.

Response:

We have made the change in the reference list.
2\textsuperscript{nd} reviewer comments (Ho Kim)

Comment #1:

The definition of heat and cold (RR’s for 99th to 75th percentile and 1st to 25th percentile) should be taken more carefully. How robust are the results by changing this criteria? (What if you compare 1st to 90th percentiles?) Graphically presenting non-parametric relationships between temp and ER visits would be informative to understand the choice of this criteria. It is well known that morality shows J or V shape with temperature. I’d like to see the shapes of the association.

Response:

First, we chose the definition of heat and cold temperatures based on a previous study that was conducted in Canada which showed that the use of the current percentiles is appropriate. This manuscript is cited in the methods section when we discuss the use of these percentiles.

Secondly, we have added two figures showing the three dimensional relationship between temperature and emergency room visits for cardiovascular diseases and respiratory diseases for each temperature values along lag days. We believe that these additional figures are addressing the reviewer’s comment. We have also added the following text at the beginning of the results section in order to briefly explain these graphs: “In appendix, Figures 1 and 2 are showing three-dimensional graphs of the relative risks of emergency department visits for cardiovascular and respiratory diseases by temperature (°C) and lag days. These graphs show that the effects of hot temperatures on emergency room admissions are generally seen within a few days of the hot day while the effects of cold temperatures are more delayed in time.”

Comment # 2:

* There is no description about Table 2.

Response:

We have added the following underlined text to the first paragraph of the results section in order to describe Table 2: “A total of 292,666 and 562,738 ER visits for cardiovascular and respiratory diseases, respectively, occurred during the study period in Toronto (Table 2). The most frequent comorbid health conditions for cardiovascular disease ER visits were diabetes (7.3\%) and cardiac diseases (6.5\%) while respiratory infections (4.0\%) represented the most frequent comorbid health condition among respiratory ER visits.”

Comment # 3:
* Reference 29 and 31 are identical.

Response:

We have corrected this issue.

Comment # 4

* First paragraph of the result on page 9: Air pollutants and weather variables are usually correlated. It's better to present the ranges of Pearson correlations and p-values in the text. NO2, CO, and O3 are always adjusted in the model. I am curious how much the results are changing depending on the choice of the air pollutants.

Response:

We thank the reviewer for raising this point as it is an error in the text. We have now added the following sentences at the beginning of the results section in order to describe the Pearson correlation coefficients: “Pearson correlation coefficients showed that CO (r = -0.11), \( \text{SO}_2 \) (r = -0.07) and \( \text{NO}_2 \) (r = -0.20) were negatively correlated with mean temperature (p values < 0.001) while \( \text{O}_3 \) (r = 0.34) and \( \text{PM}_{2.5} \) (r = 0.42) were positively correlated with mean temperature (p values < 0.001). Pearson correlation coefficients ranged from -0.07 to 0.58 when investigating collinearity between air pollutants (p values < 0.001)”.

The choice of using NO2, CO, and O3 in the models was based on the best model fit statistics obtained. However, we can reassure the reviewer that the relative risks did not change much (< 3 % change) when removing or adding other pollutants to the models.