Author's response to reviews

Title: Associations between Air Temperature and Cardio-Respiratory Mortality in the Urban Area of Beijing, China: A Time-Series Analysis

Authors:

Liqun Liu (liqun.liu@helmholtz-muenchen.de)
Susanne Breitner (susanne.breitner@helmholtz-muenchen.de)
Xiaochuan Pan (xcpan@hsc.pku.edu.cn)
Ulrich Franck (ulrich.franck@ufz.de)
Arne Marian Leitte (arne.leitte@ufz.de)
Alfred Wiedensohler (alfred.wiedensohler@tropos.de)
Stephanie von Klot (klot@helmholtz-muenchen.de)
H.-Erich Wichmann (wichmann@helmholtz-muenchen.de)
Annette Peters (peters@helmholtz-muenchen.de)
Alexandra Schneider (alexandra.schneider@helmholtz-muenchen.de)

Version: 2 Date: 11 April 2011

Author's response to reviews: see over
Dear Editors of Environmental Health,

Please find enclosed the revised manuscript “Associations between Air Temperature and Cardio-Respiratory Mortality in the Urban Area of Beijing, China: A Time-Series Analysis”. We would like to thank you very much for the comments by you and the reviewers. We have revised the manuscript addressing all comments and concerns raised by the reviewers and provide point by point responses below. We numbered each point as comment 1 (C1), response 1 (R1), and so on. We also revised the manuscript regarding the suggested formatting issues.

All authors have read the manuscript, approved submission and accept responsibility for the contents of the manuscript. There exists no conflict of any competing financial interest regarding the submitted article. The data and the manuscript are original work, have not previously been published and are not being considered for publication elsewhere in whole or part in any language except as an abstract. No similar paper is in press or under review elsewhere.

Please address all correspondence regarding this manuscript to:
Liqun Liu
Helmholtz Zentrum München - German Research Center for Environmental Health
Institute of Epidemiology II
Ingolstaedter Landstrasse 1
85764 Neuherberg, Germany
Phone: +49 89 3187 3660
Fax: +49 89 3187 3380;
Email: liqun.liu@helmholtz-muenchen.de

Yours sincerely,
Liqun Liu

POINT BY POINT RESPONSE

Reviewer 1: Massimo Stafoggia

Major Compulsory Revision –

Comment 1 (C1): “The major limitation of the study is, in my opinion, the mixing of the effects of warm and cold temperatures on cause-specific mortality. The authors carry on year-round analyses in which the cold and warm temperature terms are only defined on the basis of different lag structures. The result of this analytic strategy is that, more than likely, a residual confounding of heat is present in the study of cold temperatures and mortality and, similarly, a residual confounding of cold is present in the high temperatures analysis.”

I would suggest the authors to solve this problem in one of two alternative ways: 1) doing only season-specific analyses. ...2) doing year-round analyses in which the two terms are put together, so to estimate independent effects. In this case, however, the two terms should be made uncorrelated by applying the cold temperature term only on days below a pre-specified cut-point (maybe the median), and by applying the warm temperature term only on days above that threshold.”

Response 1 (R1): We thank the reviewer for this valuable advice. We decided to follow the first suggested approach and re-analyzed our data within warm and cold periods separately. Accordingly, we changed the Methods and Results sections in the Abstract on page 3 of the revised manuscript. Moreover, we added that “we explored the effects of air temperature on
mortality within warm period (April to September) and cold period (October to March) separately” to the Statistical analyses paragraph of the Material and Methods section on page 8. Based on the re-analyses, we estimated the exposure-response functions for temperature using penalized splines with four knots, instead of six knots (see the same section, page 9), as the temperature ranges in either warm or cold period are smaller than for the whole study period. Moreover, the periods for the sensitivity analyses including air pollution concentrations were also changed according to the separation of warm and cold season, see page 10. We also re-organized Tables 1, 2, and 3 in the revised manuscript and deleted Table 4, as it was no longer necessary. Further, we revised Figures 2 and 3, now presenting the exposure-response functions and PDL curves for temperature and cardiovascular as well as respiratory mortality in the warm and cold period separately. Based on these changes, we also re-structured the Tables and Figures in the Supplemental Material. Correspondingly, we re-wrote the Results as well as the Discussion sections in the revised manuscript on pages 10 to 14. The relative risk values used when comparing our results with results from other studies were also changed; see sections Discussion-Heat effects on page 14, and Discussion-Cold effects on page 16.

Minor Essential Revisions –

C2: The authors did not explain why they chose lag 0-1 and lag 0-14 for warm and cold temperatures, respectively. It seems an a priori choice based on previous studies, but it should be better stated. An alternative way would be to do the PDL analysis first, and then choosing the “optimal” lag afterwards, to be used in the following analysis. Did the authors consider this option?

R2: We thank the reviewer for pointing out that we poorly stated our choice of the lag 0-1 and lag 0-14 average temperatures. The focus on lags 0-1 and 0-14 was chosen on previous studies in Europe, Northern America, and other places. In the revised manuscript, we now supplemented the statement with some references (page 9): “We considered the mean of lags 0 to 1 and of lags 0 to 14 for air temperature exposure. The focus on these averages was chosen on the basis of previous studies conducted in Europe, Northern America, and other places around the world [13, 20-22].” We did not consider the second option of doing a PDL analysis first, and then choosing an “optimal” lag afterwards.

C3: The exposure-response functions display very smooth shapes, so that it is very difficult to say that it is J-shaped in some cases and linear in others. In addition, the choice of 23°C as threshold based on visual inspection seems too much arbitrary. I would suggest the authors to support this choice in more analytic ways (LR test, segmented regression, etc.), and to perform some sensitivity analyses to show how the main results and conclusions are affected by different choices of the threshold.

R3: After the re-analysis for warm and cold periods separately, only the exposure-response function between 15-day average temperature and respiratory mortality in the warm period still showed a J-shape curve, see Figure 2 of the revised manuscript. We chose the respective threshold temperature based on minimizing the Akaike Information Criterion (AIC) for a range of different threshold values. The “optimal” threshold temperature obtained by this approach was 21.3°C. Threshold temperatures detected by slightly higher AIC values were 21.1, 21.2 and 21.4-21.7°C. When using them, the heat effects of 15-day average temperature on respiratory mortality of the whole population as well as of elderly people in the warm period all became slightly weaker; the size of the effect on elderly people was still higher compared to the whole population. Please see the Materials and Methods section, Sensitivity analyses paragraph, on page 10, as well as the Results section, Sensitivity analyses paragraph, on page 13 of the revised manuscript.
C4: Authors should report the figures on total number of deaths for all causes, to offer a comparison over which to base the cause-specific figures. In particular, the cause-specific daily mean numbers of deaths seem too small for a population of almost 10 million subjects, both considering all ages together and considering only elderly subjects.

R4: We would like to thank the reviewer for raising this question. We checked again the procedure through which the Beijing CDC collects the mortality data. Beijing CDC collects the death information of all registered permanent residents of Beijing; the death information of people who reside, but are not registered in Beijing, is collected by other provinces of China. This reduced our actual study population to approximately 7 million (Beijing Statistical Yearbook 2005, http://www.bjstats.gov.cn/tjnj/2005-tjnj/content/m3-1.htm) instead of 10 million, see the first paragraph of the Materials and Methods section. According to the Beijing Statistical Yearbook 2005, heart trouble, cerebrovascular disease, and respiratory disease were the 1st, 3rd, and 4th causes of death for the population of the urban area of Beijing; the death rates were 99.24, 83.32, and 40.27 per 100,000 people, respectively. Based on this information, the daily average death counts due to cardiovascular and respiratory diseases in 2004 (366 days) could be calculated as follows:

Daily average cardiovascular death = (99.24+83.32)/100,000*7,072,000/366≈35;
Daily average respiratory death = 40.27/100,000*7,072,000/366≈8,

where 7,072,000 is the actual number of registered permanent residents in the urban area of Beijing in 2004. The obtained numbers are in agreement with the numbers we showed in the original manuscript, Table 1.

C5: In my opinion, the results reported in Table S3 are overstated in the text. The most important things to note are that there are no relevant changes for lag 0-1 temperature effects with or without adjustment for particle air pollution, and that there is a drop in the effects of lag 0-14 temperature on some mortality outcomes when adjusting for lag 2 particulate (either PM2.5 or UFP). As a consequence, the sentence in the abstract (lines 17-18) should be removed because it is not supported by the results.

R5: According to the reviewer’s suggestion, we repeated the sensitivity analyses adjusting for two-day lagged particulate pollution only, as also stated in the paragraph on sensitivity analyses, see page 10 of the revised manuscript. Based on the new results, we re-organized Table S3 and also re-wrote the Results section on sensitivity analyses on page 13 according to the reviewer’s suggestions. We have deleted the relevant sentence in the Abstract.

C6: The result on respiratory mortality and lag 0-14 temperature in winter is not credible (Table 4): low temperatures are protective for the risk of respiratory mortality???

R6: We thank the reviewer for this very good point. Actually, we also struggled with this result, although similar results have been observed previously in the Netherlands (Kunst et al., 1993). However, even after the re-analyses for cold periods only, the exposure-response functions between 2-day or 15-day average temperature and respiratory mortality still could be considered as positively linear. We therefore tried to find out more on the exposure-response functions for 2-day or 15-day average temperature and mortality due to influenza and pneumonia (J10-J18) and chronic lower respiratory diseases (J40-J47). These were the two major sub-categories of respiratory mortality in our data (we did not consider these categories for the main analyses, because of too small numbers of daily deaths, see also the last sentences of the Material and Methods section, paragraph on mortality data). Interestingly, we observed different effects regarding the two mortality categories. Whereas a decrease in temperature was associated with an increase in mortality due to influenza and pneumonia (as expected), we found opposite effects for mortality due to chronic lower respiratory diseases.

In a previous study, Hampel et al. [35] have reported differences in the associations between a temperature decrease and several blood markers of inflammation and coagulation in patients with coronary diseases and patients with pulmonary diseases. They hypothesized
that there might be different disease patterns as well as patient characteristics and medication responsible for the observed differences in the effects. Nevertheless, although we have no hint of a higher misdiagnosis for respiratory deaths than for deaths due to other causes, we cannot rule out this possibility.

Based on this additional information, we changed the corresponding paragraph on page 16-17 to: “Our study showed effects of increasing temperature on respiratory mortality even during cold season. This is contrary to our initial hypothesis, although the same situation has been observed by Kunst et al. [34] in The Netherlands. We therefore investigated the exposure-response functions between 2-day or 15-day average temperature and mortality due to influenza and pneumonia (J10-J18) and chronic lower respiratory diseases (J40-J47) (data not shown). Interestingly, we observed different effects regarding the two mortality categories. Whereas a decrease in temperature was associated with an increase in mortality due to influenza and pneumonia (as expected), we found opposite effects for mortality due to chronic lower respiratory diseases. In a previous study, Hampel et al. [35] have reported differences in the associations between a temperature decrease and several blood markers of inflammation and coagulation in patients with coronary diseases and patients with pulmonary diseases. They hypothesized that there might be different disease patterns as well as patient characteristics and medication responsible for the observed differences in the effects. Nevertheless, although we have no hint of a higher misdiagnosis for respiratory deaths than for deaths due to other causes, we cannot rule out this possibility.”

Review 2: Daniela D'Ippoliti

Major Compulsory Revision –

C7: Even if the paper is well written, however some assumptions in the analysis make it difficult a clear interpretation of the results. The authors performed their main analysis considering the whole study period for the whole range of temperature. Then they applied two different temperature variables for exposure (2-day average and 15-day average mean temperature) and interpreted the findings as “heat effect” and “cold effect” respectively. This approach is not properly right because in this case the estimates represent only the average effect of temperature on 2 or 15 days while they attributed the “cold effect” to the inverse association founded, and this is simply an artifact. Furthermore, considering the whole range of temperature, the effect could be underestimated in each case. Furthermore the authors investigated the lagged effect of temperature up to 29 days for the whole study period, warm and cold period and reported the RR of mortality in association with an IQR increase of temperature. Also in this case it is difficult to separate and to interpret the heat and cold effect for the whole study period considering an unique IQR of temperature.

For all these considerations, we suggest to the authors to report their analysis for the two periods separately.

R7: We would like to thank the reviewer for these comments. We followed the reviewer’s suggestions to report our analysis for the two periods separately. For more details, we would like to refer to Response R1.

C8: The authors founded similar results for respiratory causes using 2-day and 15-day exposure. In this case they defined this as a “heat effect” in both cases (line 23 regression results section; fig. 2 and table 3 RR=0.859 15-day as “heat effect”), but they found the same results in the cold period (table 4 RR=0.884 15-day cold period). These results suggest that in the cold period for decrease in temperature mortality for respiratory causes decreases. These finding somewhat surprising and hard to interpret, and show an opposite relationship when compared with findings of other studies in the literature where a declining temperature is associated to an increase in respiratory mortality.
If this is the case for Beijing, the authors should discuss the plausibility of these findings. Therefore the authors should revise the analysis and discuss more in depth the interpretability of their results and main conclusions.

R8: We thank the reviewer for this point. Actually, we also struggled with this result, and therefore, did further analysis regarding sub-categories of respiratory mortality. Please see Response R6 for more details on this issue.

Minor Essential Revisions –

C9: Authors should give a more exhaustive description about the population of Beijing in table 1, for instance including the age-structure. The figures in the daily deaths for each cause (ranging from 7 to 40 for respiratory and cardio-respiratory respectively) seems to be low for a population of about 9,500,000 persons.

R9: We would like to refer to Response R4 for this point.

C10: In the analysis of the lagged effects the authors reported the RR for IQR of increase in temperature, without describing the values of the percentiles. They should include the 25th and 75th percentile of temperature in table 2.

R10: In the revised manuscript we now included the 25th and 75th percentiles of temperature in Table 2. Nevertheless, we decided to present the effects for a 5°C change in temperature throughout the revised manuscript.

C11: In the text, when the authors described the analysis with PDL models, they should add that the estimates are reported RR for IQR of increase in temperature, while in the first part they expressed results as RR of mortality per 5°C increase/decrease in temperature.

R11: As stated above, in the revised manuscript we included the 25th and 75th percentiles of temperature in Table 2 now. However, to be consistent throughout the revised manuscript, we now report the lagged effects obtained from PDL models also for a 5°C increase in temperature, see Figure 3 and Supplement Material, Figure S4.

C12: In the section Results, the authors stated that for the age group 15-64 years the seasonal pattern is “no obvious”. This statement is unclear, and it would be interesting to know these results because the effects on younger populations are little known in the literature.

R12: To make our statement clearer, we added the time-series plots of daily death counts for the age group 15-64 years to Supplement Material, Figure S1. However, as no seasonal pattern can be observed we chose not to analyze that age group in more detail.

C13: The authors selected the temperature breakpoint at 23°C only by visual inspection, but this value could be confirmed with a more rigorous approach (i.e. segmented regression).

R13: We would like to refer to response R3 for this point.

C14: In the Discussion, the authors should discuss and give hypothesis to explain their results for respiratory mortality.

R14: We thank the reviewer for this comment and would like to refer to response R6.
Reviewer 3: Shakoor Hajat

C15: One striking result is the apparent non cold effect at long lags on respiratory mortality. This seems odd and warrants some discussion. For example, is misdiagnosis of respiratory deaths in elderly a potential problem here?

R15: Please see response R6 for this issue. Although we have no hint of a higher misdiagnosis for respiratory deaths than for deaths due to other causes, we cannot rule out this possibility.

C16: Although acknowledged as a limitation, I think the use of only 1 monitor also needs further reflection. Can the authors give a sense of how much temperature may vary in a big city such as Beijing? Might the heat threshold be at different values for different parts of the city?

R16: We thank the reviewer for this comment. We obtained further data on daily meteorological parameters from an internet service (Weather Underground 2011). Data from the two sources showed a good agreement ($r > 0.99$ for air temperature); please see also Material and Methods, paragraph on meteorological and air pollution data. The other monitoring site is located in the center of Beijing, but contains missing values; otherwise it would have been an alternative for our analyses.

C17: 40 cardio-respiratory deaths per day seems comparatively low for a city of 10 million people. Do the deaths provide 100% coverage or just a fraction of the population – in which case, could this introduce selection bias?

R17: We would like to refer to response R4 for this comment.

C18: I think some of the explanations could be clearer in places; for example:
- Abstract, results. The heat threshold used should be specified when quoting the RR here.

R18: We thank the reviewer for this suggestion. We have mentioned the threshold temperature, but we didn’t quote the RR of 15-day average temperature’s increase in the warm period.

C19: Abstract, results. “Ultrafine particles may play a role in combination with temperature...” This implies that the authors assessed possible interactive effects between the two exposures, which I do not think was done. In a city such as Beijing, where pollution levels are so high, possible synergistic effects would have been an important issue to address.

R19: We have deleted this sentence in the revised manuscript. We thank the reviewer very much for addressing the issue about synergistic effects here; however we think that this additional analysis goes beyond the scope of this manuscript and would increase the length of this manuscript enormously. We appreciate this comment a lot and will consider it for further analyses.

C20: Statistical analyses. “The absolute value of the sum of the partial autocorrelation...” The authors should clarify that they mean summation to zero of individual lags.

R20: We thank the reviewer for this comment. We have clarified these issues in the revised manuscript on page 9: “To ensure sufficient adjustment for season and other meteorological parameters, time trend and relative humidity were forced into all models. Season, day of the week, public holidays and barometric pressure were only included if they improved model fit.”
As a criterion to guide the selection of degrees of freedom (DF) for trend, we used the minimization of the absolute value of the sum of the partial autocorrelation function (PACF) of the model’s residuals for a fixed number of lags [18]. Model selection for the other confounders was carried out by minimizing the Generalized Cross Validation (GCV) criterion [19].

C21: Justify use of lags 0-1 and lags 0-14.

R21: We would like to refer to response R2 for this point.

C22: Regression results, paragraph 3, 3rd sentence. I am not sure there is any virtue in referring to a possible long-term harvesting effect due to accumulation of susceptible as this cannot be addressed in this type of analysis. Also, the statement that “RR<1 could be considered a combination of both real cold effect and harvesting effect” sounds unconvincing to me. All models control for season so I am not clear how this could represent a simultaneous heat and cold effect. I think much of this paragraph could be reworded.

R22: We thank the reviewer for raising this doubt. As we now present our analyses for warm and cold periods separately, we do not have the problem of distinguishing delayed cold effects and harvesting effects in the revised manuscript and were therefore able to reword the whole paragraph; please see the Results section for the updated results.