BMJ - Decision on
Manuscript ID
BMJ.2018.045335

Body:	12-Jul-2018

Dear Dr. Kan

Manuscript ID BMJ.2018.045335 entitled "Cause-specific mortality risk and burden associated with non-optimum ambient temperature in 272 main Chinese cities"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Tiago Villanueva
Associate Editor
tvillanueva@bmj.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Sophie Cook (chair), Rafael Perera (statistician), Wim Weber, Jose Merino, Elizabeth Loder, John Fletcher, Georg Roggla, Daoxin Yin, Tiago Villanueva

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
A pretty complex modelling study. This is necessary given the data and the question asked. Several of the methods used here are relatively new but seem appropriate. Nevertheless, I would like them to answer a few questions regarding these models:
1) How robust is the estimation of time lags. Is this based on an automatic selection process? How can we determine consistency of this across regions/cities?
2) The estimation of a city specific MMT and the recentering based on these, does this approach minimise potential bias or create any?
3) The lack of pollutant data is likely to be a major confounder, particularly as there are relevant interactions between pollutants and different temperatures. Unless all sites have same contamination levels, this is likely to be affecting the results.
Issues 2 and 3 stem from some lack of clarity in their Stage 2 modelling. Reviewers have relevant comments on the need for clarity in their meta-regression (meta-analysis) approach. Some of the city characteristics would need to be included here.
Generally it seems well carried out.

- Several editors were in favour since, even though the findings are in line with other studies, it is a large, descriptive study that covers most of China and is in line with BMJ's interest in climate change.

- One editor suggested that you discuss the potential impact of central heating in Northern China (areas in the north of the Yangtze River) during winter, even though data might be limited. And it might be more reader-friendly if you can mention in the abstract the temperature range in Degree/Fahrenheit for "moderate cold", "moderate heat", etc.

- Another editor said that even though the data is national in scope, there are relatively few cities from some regions (e.g. alpine region). She wondered if you discuss more the fact why cold seems to be worse than heat overall, and that moderate cold and moderate heat are more important than extremes of either because they account for more overall exposure.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

This is an interesting study to examine the impacts of ambient temperatures on cause-specific mortality in China, with a large data set. This study provides additional evidence on the impacts of temperature on mortality in China. Particularly, the authors use a relatively complex analytical framework, involving sophisticated designs and statistical techniques. The results are neatly summarized and interpreted, and then carefully discussed. My comments mainly refer to

analytical strategies, which do not require major changes to the structure of the manuscript.

1) The Design of abstract, the current version only reflects the first stage but no information for second stage. Suggest to add statement for second stage analysis, like "Time series analysis with DLNM was used to estimate city-specific associations in the first stage, then meta-analysis strategy was applied to model the effect estimates in the second stage ".

2) The conclusion of abstract should be more specific. The current version is broad.

3) The second stage analysis is expressed a little unclearly. It is not clear which independent variables are used as predictors in the BLUP. Usually, BLUP (a special prediction function of meta-regression) is used to predict city-specific association, with city level characteristics (e.g., mean temperature, temperature range, GDP, latitude, or others).

4) Usually, national level association is pooled by meta-analysis or meta-regression with intercept only (no predictors, meta-analysis is a special case of meta-regression). It is ok that the authors use BLUP to predict national level association, but they should develop a meta-regression with city level characteristics as predictor (comment #3), then calculate the average of city level characteristics as predictor to predict national level association. Or if the authors used other method, it should be clarified. It is the same to pool regional associations.

5) "We assessed the potential effect modification by city-level characteristics on climate, geography and socioeconomic conditions." This part is a meta-regression. Actually, it can be used to predict city level association (with city characteristics), regional level association (with region as predictor), and national level association (intercept only). I suggest to use this method as the main second stage analysis. This will make the analysis clear and easy to understand by readers. However, it is optional if the authors could clarified their method clearly.

6) The scale of x-axis of Figure should be percentile at national (or regional) level association, because the authors put the spline knots at the same percentile of temperature for each city, not the absolute temperature. So the pooled association represents relative scale (percentile scale).

7) Suggest to add range of MMP and MMT into Table 1.

8) It might be good to discuss the results for age group, sex, and education level.

Additional Questions:
Please enter your name: Yuming Guo

Job Title: Associate Professor

Institution: Monash University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 2

Recommendation:

Comments:
Chen et al. quantified the disease burden due to non-optimum temperature in in 272
main Chinese cities, across different climatic zones, demographic and socioeconomic
factors. This comprehensive picture can inform public health policy and protection of
vulnerable populations in China. Improved discussion and highlights are needed on
the novelty of methodology and findings and differentiation from the earlier papers
of Gasparrini et al who have reported that:

1) Both cold and heat are associated with increased risks of mortality;
2) Moderate cold is responsible for the majority of the temperature-related disease
burden; and
3) Areas with warmer climate usually are subject to larger effects of cold, whereas
cold areas are more susceptible to hot effects.

For example, one novel contribution of the current manuscript can be the
comparison and discussion of cause-specific and system-specific (cardiovascular vs.
respiratory) disease burdens. The systemic evaluation of latitude and longitude
effects in China can also be highlighted.

Minor comments:

1.   BULP → BLUP
2.   Line 434-436: '… attributable fraction of … on …' should be a typo.
3.   Figure 5 can be improved by presenting the 3 factors separately …

References:

1.   Gasparrini A, Guo Y, Hashizume M, Lavigne E, Zanobetti A, Schwartz J,
Tobias A, Tong S, Rocklöv J, Forsberg B, Leone M, De Sario M, Bell ML, Guo YLL, Wu
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H, Armstrong B. Mortality risk attributable to high and low ambient temperature: a
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2.   Vicedo-Cabrera AM, Sera F, Guo Y, Chung Y, Arbuthnott K, Tong S, Tobias
A, Lavigne E, de Sousa Zanotti Stagliorio Coelho M, Hilario Nascimento Saldiva P,
Goodman PG, Zeka A, Hashizume M, Honda Y, Kim H, Ragettli MS, Röösli M,
Zanobetti A, Schwartz J, Armstrong B, Gasparrini A. A multi-country analysis on
potential adaptive mechanisms to cold and heat in a changing climate. Environment
International. 2018;111:239-246.
3.   Gasparrini A, Guo Y, Hashizume M, Kinney P, Petkova EP, Lavigne E,
Zanobetti A, Schwartz J, Tobias A, Leone M, Tong S, Honda Y, Kim H, Armstrong

BG. Temporal variation in heat-mortality associations: a multicountry study. Environmental Health Perspectives. 2015;123(11):1200-1207.

4.   Guo Y, Gasparrini A, Armstrong BG, Tawatsupa B, Tobias A, Lavigne E, Coelho MS, Pan X, Kim H, Hashizume M, Honda Y, Guo YL, Wu CF, Zanobetti A, Schwartz JD, Bell ML, Scortichini M, Michelozzi P, Punnasiri K, Li S, Tian L, Osorio Garcia SD, Seposo X, Overcenco A, Zeka A, Goodman P, Dang TN, Dung DV, Mayvaneh F, Saldiva PHN, Williams G, Tong S. Heat wave and mortality: a multicountry, multicommunity sudy. Environmental Health Perspectives 2017;125(8):087006.

Additional Questions:
Please enter your name: Linwei Tian

Job Title: Associate Professor

Institution: The University of Hong Kong

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 3

Recommendation:

Comments:
This paper is to quantify the cause-specific mortality risk and burden associated with non-optimum ambient temperature. They reported that 12.55% of total mortality was attributable to non-optimum temperatures and that fractions differed by death causes with 16.26% for cardiovascular diseases, 17.97% for coronary heart disease, 14.62% for stroke, 14.71% for ischemic stroke, 19.64% for hemorrhagic stroke, 10.16% for respiratory disease and 11.6% for chronic 23 obstructive pulmonary diseases. The authors applied widely used dlnm(distributed lag non-linear models) and the results are also comparable to the previous studies. Even though the study period is relatively short (2013-2015, 3 years), the authors performed large scale 272, city-wise analyses. And applied meta-regression analysis to have integrated

information from the city-wise results. This manuscript provides valuable information on this research area. I have a few comments mainly on the analytic side.

Exposure-response curve for small cities would be very instable, I expect. Do you think city is the best option for the first dlnm fitting? Bigger area than individual city, like province, would be better. What is your response?

RR(or excessive deaths) and AF have pros and cons. The authors extensively reported AF which indicates that AF would be better as an index. Please comment on this.

There are several papers indicating strong confounding of the season on the cold effect. Some even suggested that cold effect is not real, it is actually winter effect. I think most of the recent papers should be more cautious on cold effect. What do you think?

Please discuss the effect of influenza on estimating the cold effect should also be discussed.

Additional Questions:
Please enter your name: Ho Kim

Job Title: Professor

Institution: Seoul National University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 4

Recommendation:

Comments:
Based on daily numbers of deaths from non-accidental causes in 272 Chinese cities, the paper quantified the cause-specific mortality risk and burden associated with non-optimum ambient temperature. The authors performed comprehensive analyses and the statistical methods used were sound. This paper is interesting and generally written well. It added significant evidence to the literature on the contribution of ambient temperatures to cause-specific mortality. If the authors can answer all the questions given below then the paper should be reconsidered for publication.

1.Please provide more details to clarify the representativeness of the Disease Surveillance Point System of China. How many districts in each city involved in the system? The proportion of deaths registered in this system in each city, etc.

2.This study aimed to quantify mortality burden associated with non-optimum ambient temperature, while the authors only considered non-accidental deaths, probably leading to an underestimation of the burden. Is the reason for excluding accidental deaths that significant effects were not found? Several studies in US, Korea and China have reported the association between suicide mortality (one of main causes of accidental deaths) and ambient temperaturse. It would be of great interest to further investigate in this large-scale study. I suggest reporting relevant results anyway.

3.Page 7, lines 86-90, How to divide five climatic zones? Is it a common way? Any references for this division? Please add some description of weather conditions in five climatic zones.

4.Line 172 "univariable multivariate meta-regression models", What does it mean? "Each model included a single meta-predictor", do you mean that each potential effect modifier was analyzed separately? Why not perform multivariate meta regression? The climate, geography and socioeconomic conditions under consideration are correlated. In addition, the sources of these demographic and socioeconomic data should be mentioned.

5.Both MMT and effect estimates varied by city. The authors clearly showed the impacts of climate and socioeconomic on the heterogeneity in effect estimates. MMT is an important indicator of the population's adaption to ambient temperature. It would be interesting to describe its geographic variations and give some explanation, too.

6.Figure 2. The overall lag structure of extreme cold effects. The trailing end of the curve goes upwards and shows significant effects even at lag 15 and afterwards. How do you explain this?

7.Page 9, lines 138, BLUP was mistyped as BULP.

8.Page 16, lines 278-282, according to Figure 4, the distribution from tropical monsoon zone seemed not to be similar with that from temperate continental zone.

9.Page 43, the labels of x axis in two bottom figures should be lag(day).

Additional Questions:
Please enter your name: Chun-Quan Ou

Job Title: Prof.

Institution: Department of Biostatistics, School of Public Health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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