

Author's response to reviews

Title: A Review of the Epidemiologic Evidence of High Ambient Temperature and Mortality Accounting for Air Pollutants and Identifying Vulnerable Subgroups

Authors:

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Version: 3 **Date:** 20 May 2009

Author's response to reviews: see over

May 20, 2009

To: The Editor of the Environmental Health
Re: MS# 7301135002573224

Please find attached the manuscript entitled "High Ambient Temperature and Mortality: A Review of Epidemiological Studies from 2001 to 2008" for your consideration in Environmental Health (note: title changed from original submission). Please find a point-by-point italicized response to the editor's and reviewers comments below, and the manuscript with tracked changes. All comments were very helpful in strengthening this manuscript, and I feel the questions and concerns were sufficiently addressed.

I thank you for the opportunity to resubmit this manuscript, and look forward to hearing from you soon.

Sincerely,
Rupa Basu, PhD, MPH

Editor's comments:

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

In addition, please note that a review does not require a structured abstract.

Abstract deleted.

Please specify the 'issues' you refer to on page 3 line 10.

Epidemiologic studies (not issues)—clarification made.

Add reference 1 after 'the previous review' (page 3 line 11) so that it's clear what you refer to.

Basu & Samet reference added.

Harvesting should be briefly explained when first mentioned (page 4 line 2).

Good point. The following sentence was moved up, "Mortality displacement (also known as harvesting) refers to the phenomena suggesting that observed deaths from some environmental exposure occur in the most frail individuals whose deaths have only been brought forward by a few days."

The section on case selection needs to be rewritten for clarity, and the first sentence may need a reference if kept.

The first sentence was clarified into 3 separate thoughts/sentences.

Please state why multi-city analyses are preferred (page 7 line 7).

Multi-city analyses are preferred, since bias from a single city analysis may result and the findings from multiple areas may be more generalizable (in text).

The connection between temperature-humidity and acclimatization is not clear (page 8, lines 5-6).

I agree that the part about acclimatization is confusing here, so I took it out, since there is some discussion about it in the conclusions section.

Please explain the 3.12% on page 8 line 9.

3.12% refers to a 3.12% increase in daily mortality, which was added to the text for clarification.

The conclusion on page 9 lines 2-4 needs to be justified.

The conclusion was put at the end of the section, after an explanation of the results.

Given the larger number of different outcomes (page 10, lines 4-8), would it not be better to focus on those that are most plausible or most important?

These are actually a "shortened" list, based on the most plausible and also the ones that are included in most studies.

In the explanation on harvesting, delete the last four words on page 11, line 23.

The sentence about "economic evaluation" was deleted.

The Conclusions says that outcomes and vulnerable subgroups 'have not been identified previously' - please clarify what is meant.

Text changed to: "...have not been identified in previous epidemiologic studies of ambient temperature."

The tables need to be restructured. The sequence of studies is unclear - please state the criteria (year of publication may be an option).

Year of publication then alphabetical order, added to summary of studies section.

The three tables overlap, and it is unclear why some studies appear in more than one table, others not. If the revised table(s) cannot fit the portrait format, please upload as 'additional file'.

I revised the tables. There is overlap, only if one study looks at two separate categories, such as air pollutants as confounders and vulnerable populations.

Please also ensure that your revised manuscript conforms to the journal style (<http://www.ehjournal.net/info/instructions/>). It is important that your files are correctly formatted. Use the proper symbol for degrees and subscripts for chemical symbols like ozone (O₃, where 3 should be subscript). The same for PM fractions. The section with Abbreviations (correct heading) should be in a single paragraph. The disclaimer from 'Competing interests' should be moved to 'Acknowledgements'. Remove 'Author's information'. In the revised version, please remove line numbering on each page and page numbers. Initials should be used in Author's Contributions not full first and last name.

All of the above have been changed accordingly.

Reviewer's report

Title: A Review of the Epidemiologic Evidence of High Ambient Temperature and Mortality Accounting for Air Pollutants and Identifying Vulnerable Subgroups

Version: 2 **Date:** 23 March 2009

Reviewer: Paola Michelozzi

Reviewer's report:

This article addresses a relevant topic since it revises the most recent evidence about the association between high temperatures and mortality. Overall, I recognize there is a substantial work behind this literature review but for being a systematic review, the rationale and the selection procedures should be more carefully defined (I advise to refer to the Cochrane guidelines). Specifically, the review's objectives should be better defined and the study designs more appropriate for answering the specific question should be briefly described. For example, case-crossover and case-only analyses are more suitable to study the vulnerability factors to heat-related mortality.

Moreover specific section of the paper, i.e. Vulnerable subgroups, is examined rather superficially. Epidemiological studies on heat waves episodes produced important results on vulnerable subgroups and should be considered in this section.

Therefore, I believe that the work is potentially of interest but substantial revision taking into account the following major problems is necessary.

Major problems

1. Title should be revised. I suggest "High ambient temperature and mortality: review of epidemiological studies from 2001 to 2008"

Title is changed as suggested.

2. Page 1-4, Abstract and Background and Methods: The research question should be more detailed and better addressed by the rationale and methods section.

Since the journal does not require an abstract for review articles, the abstract was deleted.

3. Page 1, Abstract, Results, lines 10-13: this paragraph should be moved in the Methods. Results should report the number of studies selected by the search strategy and the number of studies included for each topic of interest.

Since the journal does not require an abstract for review articles, the abstract was deleted.

4. Page 1, Abstract, Results, lines 13-16: should be moved at the end of the Paragraph

Since the journal does not require an abstract for review articles, the abstract was deleted.

5. Page 3, line 22, Background: Aims and, more thoroughly Methods (page 4) should include the justification for excluding some types of epidemiological studies and for including others. The type of studies selected should reflect your research question. Furthermore, has the quality of studies included in the revision been evaluated in any way?

The following sentences were added to the selection criteria for clarification: "All studies included in this review were published in peer-reviewed journals... In addition, Tables 2 and 3 had the keyword "air pollutants," "ozone," and "particulate matter" added, and Table 4 and 5 had "vulnerable" or "susceptible groups" added. ... The review focused primarily on quantitative studies of ambient temperature, primarily consisting of studies using the time-series and/or case-crossover methods. The outcomes from these studies reported a regression coefficient, relative risk, odds ratio, or percent change in mortality, along with a standard error or confidence intervals. Studies that reported mortality counts or excess deaths following heat waves were excluded so that the focus remained on general ambient temperature exposure in a variety of locations, rather than on short time periods."

6. Page 4, Methods: The research strategy was too simple, and you have missed several studies of potential interest for your three topics.

A few more studies that were added to this review: Vaneckova 2008 (2 studies), Barnett 2007, El-Zein 2004, Goodman 2004, and Pattenden 2003.

7. Page 4, Methods, line 9: the inclusion criteria are unclear and study design more suitable to your research question should be defined more clearly (i.e. time series studies, case-crossover studies, etc.) The inclusion/exclusion criteria for studies regarding each topic of interest (the same summarized in the tables) should be included. The paragraphs "exposure assessment", "case selection" and "study design" should be included in a section "Methodological issues", as well as the paragraph "Harvesting" (see pag. 11 lines 13-23) .

Methods is changed to Methodological issues with harvesting also included in this section, and all of the suggestions were all implemented.

8. Page 7, Summary of recent studies: For each topic the number of studies selected and a brief description of them should be reported (i.e. the number of time series or case-crossover studies, the number of studies from the US, Europe, other countries)

Good suggestion. Number of studies for each category was added.

9. Page 7, Summary of recent studies, General ambient temperature and mortality: The paragraph is biased since several studies are not included. You

should distinguish between results from the different study designs. A few studies were added, as mentioned. In addition, the studies are separated by case-crossover and time-series.

10. A revision of Table 1 is essential. According to the publication period you considered, you should add several other time series studies on the effect of high temperatures on mortality for all causes (see appendix). The results should be better synthesized, giving more homogeneous information for each study, leaving only the most relevant results, and providing the threshold values. You stated that “Studies that reported mortality counts or excess deaths following heat waves were excluded” but in table 1 there are three studies on heat waves analysis (Conti et al. 2005, Grize et al. 2005, Le Tertre, 2006). Moreover, it is questionable to insert Davis et al. 2003 since it employed a different methodology from all other studies included in the table.

I did not see the appendix that the reviewer is referring to, but added some more studies, and changed the title to include daily mortality. Also deleted the studies on heat waves from the review, and the Davis et al study, since they did not meet the study inclusion criteria.

11. Page 8, Summary of recent studies, Air pollutants as confounders/effect modifiers: Results both in table 2 and in the text should be presented separately for each pollutant. You should check for possible articles missed (see major problem 2). Check also for Dear et al. 2005 (reference 16) since it seems an episode analysis of heat wave.

Tables have been redone and are now separated into 2a, 2b, 3a, and 3b to separate by pollutant (ozone and particulate matter) and also by study design. I also deleted the Dear et al. 2005 study.

12. Page 9, Summary of recent studies, Cause-specific outcomes and vulnerable subgroups: In this paragraph the subject “vulnerability subgroups” is biased and incomplete. Several studies are not included (see major problem 2). Moreover, one of the most important aspects concern chronic conditions that increase susceptibility to high temperatures, and this aspect was not considered. This paragraph demands an in-depth examination, and probably should be omitted from this review.

The vulnerable subgroup is an important finding, so the paragraph was kept, but I added some additional studies.

13. Table 3: If included, should be revised.

Revised by study design into the new Tables 4 and 5.

14. Page 11, Summary of recent studies, Harvesting: This subject was not

introduced in the background and methods sections. The first part of the paragraph should be moved in the section “Methodological Issues”. Furthermore, you should check for the types of studies you included since references 39-41 are studies about heat waves and Schwartz et al. deals with hospital admissions and not with mortality. You should include in this paragraph also the following articles that evaluated the harvesting effect:

- Braga et al. 2001 (your reference 59)
- Braga A.L.F., Zanobetti A, and Schwartz J. The Effect of Weather on Respiratory and Cardiovascular Deaths in 12 U.S. Cities. Environ Health Perspect 110(9), 859-863. 2002.
- Baccini et al. 2008 (your reference 7)
- Hajat S, Kovats R, Atkinson R, Haines A. Impact of hot temperatures on death in London: a time series approach. J Epidemiol Comm Health 2002;56:367-372.

I added all of these studies to the references, and also kept the Schwartz study because of the methodology that used to address harvesting. I also moved the harvesting section under methodological issues, since I agree that it's a better fit.

15. Page 13, Discussion: Avoid to draw conclusions from evidence that is contrasting and limited as in the case of studies about air pollution (drop the sentence “In other words, the association between temperature and mortality is partially a result of confounding by PM and O3”). Discuss the possible mechanisms through which the different pollutants should be confounders or effect modifiers of the temperature-mortality relationship in more detail.

I deleted the sentence. The PM and O3 already had some mechanisms added to the conclusions section, and I added a couple more sentences.

16. Page 15, Discussion, lines 5-16: The entire paragraph is out of place here since your focus is on mortality. I advise you to drop the paragraph. If you decide to leave it, check for having included all relevant references. In particular, a multicentre study on heat-related hospital admission has recently been published and should be cited (Michelozzi P et al. Am J Respir Crit Care Med. 2009 Mar 1;179(5):383-9.), while Schwartz et al. 2005 should be dropped since it is a case-only analysis of deaths among patients with previous hospital admissions for heart and lung disease.

Agree that the morbidity paragraph is out of place, so I deleted it, along with the case-only studies (including Schwartz).

17. Furthermore, the discussion about possible limitations of the present review is missing.

*I added a paragraph on the limitations of this review:
“This review, however, has several limitations. While it includes the most recent epidemiologic studies using time-series and case-crossover methods, it does not*

include studies of heat waves or studies using other approaches in an effort to focus on general ambient temperature over longer time periods. Both methods rely on ecologic exposure variables for temperature, and the time-series analysis also uses aggregated counts of mortality. Thus, an advantage of the case-crossover study is that differences by individual-level characteristics such as age, race/ethnic group, gender can be analyzed. Although the methods used across studies were similar, it was still often difficult to compare estimates between studies because of the analysis type (e.g., different threshold values). There were also not a sufficient number of studies to conduct a meta-analysis of the results, or other more substantial quantification. Finally, there may be some publication bias in the studies that were chosen, but by using PubMed, the bias may be limited, as it includes most scientific journals.”

18. Conclusions should be changed: You should point out the topics where your review has identified there is contrasting or limited evidence, and focus on the possible future research areas. I advise that an important point for future research is the identification of clinical pattern of chronic diseases that increase susceptibility to heat.

Added that the identification of clinical pattern of chronic diseases should be examined, particularly in the elderly as a vulnerable subgroup.

Minor problems

1. Throughout the text you should provide the appropriate references to justify your sentences.

References were added where appropriate.

2. Page 4, Methods, Exposure assessment, lines 21-23: Your speaking is more about statistical modelling than about exposure modelling. For example, you have not mentioned that most studies used data from the nearest airport station instead of data from city monitors (see de'Donato F et al. Int J Biometeorol. 2008 Mar;52(4):301-10). About this paragraph see also the Major problem 3.

Added a few sentences about exposure modeling:

Temperature data are often examined at the city or county level or measured near airport stations. Thus, misclassification of exposure may occur, especially for larger counties. However, since the bias should be non-differential (i.e., not different by county or unit of analysis), the bias in the estimate would be toward the null, where the results would be underestimated. Misclassification of exposure may be reduced in future studies by using smaller buffer zones, such as five or ten kilometers around each monitor, if sufficient data are available.

3. Page 5, Methods, Study design, line 22: This sentence is not true for Europe where a number of studies about 2003 heat wave were performed in recent years.

Added that the 2003 European heat wave studies are exceptions and were not included in this review.

4. Page 7, Summary of recent studies, General ambient temperature and mortality, line 18: avoid the generalization about the value of the threshold value from all the available studies (see major problems 6).

Point well taken. Threshold value taken out here.

5. Page 7, Summary of recent studies, General ambient temperature and mortality, line 21: the sentence is inexact, since the threshold is often identified from the visual inspection of the exposure-response curves or by mathematical (i.e. through derivatives) or statistical (i.e. by maximum likelihood) methods.

Good point. Added that the threshold value is often identified from visual inspection...

6. Page 11, Summary of recent studies, Cause-specific outcomes and vulnerable subgroups, line 7: Please clarify "lower income areas" (i.e. persons living in lower income areas).

Changed text to persons living in lower income areas.

7. Page 13, Discussion, lines 12-14: The sentence "The results from future studies can be more readily compared..." is completely wrong since the relationship between temperature and mortality during summer is non-linear.

Some studies have reported linearity for temperature, especially in the summer, but I did add that a regression coefficient would be helpful and that the studies can be more compared assuming linearity.

8. Page 16, Discussion, lines 11-20: The entire paragraph is unclear. Some of the informations that you cite cannot be retrieved by death certificates. Furthermore, this apply only to case-crossover analysis that is based on individual data. The sentence about misclassification of exposure is out of place here.

I moved the sentences about misclassification of exposure to the methodological issues, and also added here that a strength to the case-crossover analysis is that individual data can be analyzed.

9. Page 16, Discussion, line 24: I believe that health care institutions are the organisms deputated to implement policies to prevent heat-related mortality and not meteorological services like the US NWS.

Health care institutions and governmental agencies are responsible for policy (change was made), but the National Weather Service in the U.S. is also responsible for heat watch systems.

10. Page 17, Discussion, lines 2-3: No formal evaluation of heat-health watch warning systems has been performed to date. This is an important area for future research. Take into account that HHWWS are not able to reduce heat-related mortality, without a prevention plan targeting vulnerable subgroups (see the WHO guidance on Heat Health Action Plans <http://www.euro.who.int/document/e91347.pdf>).

Good point. Added that no formal evaluation of HHWWS has been made and need a prevention plan to target vulnerable subgroups to the conclusions.

11. Page 17, Discussion, lines 3-5: Support your statement “The 2003 heat wave in Western Europe resulted in 35,000 deaths, but subsequent heat waves in more recent years did not produce such detrimental effects” by the appropriate references.

Changed the text to: ...” but a warning system is being developed by the World Health Organization so that subsequent heat waves do not produce such devastating results.”

Reviewer's report

Title: A Review of the Epidemiologic Evidence of High Ambient Temperature and Mortality Accounting for Air Pollutants and Identifying Vulnerable Subgroups

Version: 2 **Date:** 1 April 2009

Reviewer: Antonella Zanobetti

Reviewer's report:

The paper is a complete review of the literature on the effect of temperature on mortality. The manuscript is well written, clear and concise.

One issue I have is that by looking at the tables it is not really possible to compare the results across studies. I understand that this is not easy due to the difference of expressing the results, but maybe some changes in the tables could be helpful.

Minor Essential Revisions

Page 5 lines 15-18: I think that what is called the “underlying cause of death” is the main cause of death, and therefore the immediate cause. There is no immediate cause of death in the death certificates.

I took out the end of the sentence mentioning the main cause of death, and kept underlying cause of death, to prevent confusion.

Page 6 lines 8-10: I understand the meaning but the phrase need to be edited to be more clear.

I restructured into two separate sentences.

Page 7 lines 19-20 the phrase is not clear. Mainly at line 20: lower values those effect...?

The end of that sentence was repetitive and should have been deleted.

Page 8 line 6: humidity levels. "Levels" is repeated from line 6 and can be deleted.

The second "levels" was deleted.

Page 8: there is no reference for the Korea study.

The Kim et al. reference was added.

page 11 lines 21-23: if there is harvesting then this would suggest that exposure influence mainly frail persons, but if there is no harvesting then it means that exposure is a real public health issue. It is not clear the phrase that ends with "several years".

The sentence about the economic evaluation was taken out, since it is not relevant to epidemiologic studies. Another sentence was added to state that if harvesting is not found, the exposure is a real public health issue.

Tables: by looking at the tables it is hard to compare the results across studies. For example the column results in the three tables is long and not clear, may be the outcome and method columns could be combined and the results could be divided in two columns or summarized better. For some references no risk is given.

The outcome in Table 1 was added to the title, since all studies examined daily mortality. In general, the tables were restructured to clarify the presentation of the risk estimates and often separated by method.

Across all the tables the method is always listed as time-series or case-crossover, only in Table 1 in the third reference the confounders are listed. Is there a reason for this? I would suggest deleting that description.

The extra description of this study was deleted.

Again in Table 1 ref 54, the method column is not clear: comparisons of counts to 2002? Moreover in the method the author write that studies who reported excess deaths were excluded, why is this study not in that category?

This point is well taken. All studies of heat waves, including this one, were excluded, since they did not meet the inclusion criteria for the study.

Discretionary Revisions

Instead of harvesting, maybe mortality displacement could be more appropriate.

Good point. The title was changed to mortality displacement, with harvesting added to the ().

Page 4 line 9: 'mortality counts' this is not clear, time series are mortality counts, but the author does include time series studies.

The sentence was divided into two, so that it is clear that the mortality counts refer to the time series studies.

Page 12 lines 10-12: maybe the effect in Delhi and Sao Paolo compared to London was also different due to different temperature pattern in the cities.

I added the different temperature patterns between the cities as a possible explanation.

REFERENCES

1. Pattenden S: *Mortality and temperature in Sofia and London*. 2003.