Author's response to reviews

Title: Hourly Differences in Air Pollution and Risk of Respiratory Disease in the Elderly: A Time-Stratified Case-Crossover Study

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Author's response to reviews: see over
Responses to comments from Dr. Annunziata Faustini

Thank you very much for your positive evaluation and valuable comments. Our responses to your comments are described below in a normal font following your comments in boldface.

COMMENTS TO THE AUTHORS
I read this R1 version of the manuscript with pleasure and I have to acknowledge that the authors have adequately answered each of the many points I raised. Consequently, in my opinion the paper is now suitable to be reconsidered for publication. However, I would still suggest that the authors improve the discussion. This is a feasible request and would make the paper more appropriate for a journal like Environmental Health.
There are specific points on which I would like to draw the attention of the authors:

# Though the authors justified the choice of studying respiratory effects in the elderly maintaining their strongest effect on that age group, I would suggest that the authors indicate this choice in the paper’s title, to avoid the impression that they neglected the important effects reported in children.

Reply:
Thank you for your suggestion. We clarified it in the title and the abstract:

“Hourly Differences in Air Pollution and Risk of Respiratory Disease in the Elderly: A Time-Stratified Case-Crossover Study” (Title)

“We evaluated the associations between hourly changes in air pollution and the risk of respiratory disease in the elderly, using the time of the emergency call as the disease onset for each case.” (Background in Abstract)

# More attention has to be paid in the discussion to the differences between the SPM and respirable fraction of particles (PM10) included in the SPM. It could be difficult to compare the results when they are used alternatively, and most papers use the respirable fraction.

Reply:
Thank you for your suggestion. Actually, SPM is considered as PM7 in this
study. We clarified it again at the beginning of the Discussion section and provided some discussions as follows:

“We found that SPM (PM$_7$) exposure 24 to <72 hours prior to the onset and ozone exposure 48 to <96 hours prior to the onset were associated with the increased risk of respiratory disease….”(p.12, lines 3-5)

“The observed respiratory effect of SPM, ozone, and SO2 are consistent with previous findings [2, 5]. To interpret the finding, one point should be noted that SPM (PM$_7$) are particles larger than PM with less than 2.5 µm (PM$_{2.5}$) but smaller than PM with less than 10 µm (PM$_{10}$); thus, SPM is also included in the range of respirable fraction.” (p.12, lines 10-14)

# Some comments are needed about the results of many sensitivity analyses which don’t change the results. The consequences for the main methods adopted would make an interesting discussion.

Reply:
Following your advice, we added some comments regarding sensitivity analyses as follows:

“Not adjusting for weekly numbers of reported influenza cases also provided similar results (data not shown), which implies that influenza epidemics did not confound the association between short-term exposure to air pollution and respiratory health effects.” (p.11, lines 16-19)

“Although we used a definition of pneumonia and influenza together, 97% of the patients (n=3,116) were diagnosed pneumonia or lower respiratory infection (LRI); thus, the effect estimates obtained for pneumonia and influenza would be attributable to LRI. Indeed, when we excluded influenza cases from the analysis, the result did not change substantially.” (p.14, last line - p.15, line 4)

# The authors cannot disregard the negative results of effect modifiers, in particular previous diseases on the relationship between SPM and respiratory diseases, and gender on the relationship between ozone and respiratory diseases.

Reply:
Thank you for your comment. As you pointed out, some findings on effect
modification are not consistent with previous studies. Following your comment, we amended a paragraph on effect modification in the Discussion section as follows:

“We also observed that several patient characteristics were associated with increased risk of air pollution. The higher effect estimate for women of the association between ozone exposure and respiratory disease is consistent with a multi-city study in Asia [35], a study in Massachusetts, US, did not find effect modification by sex [36]. Among preexisting diseases, we observed a statistically significant interaction only for respiratory disease: those without a history of respiratory disease had a higher effect estimate for the association of SO2 exposure with pneumonia and influenza. Although the reason is unclear and we have no other evidence, those without respiratory disease may be more sensitive to the exposure or be exposed more heavily, probably because they can stay outdoors longer. However, a previous study with a cohort of COPD patients in Italy suggested those with preexisting disease history (in particular, heart conduction disorders and cerebrovascular disease) were more susceptible to air pollution [37]. Further investigation may be needed.” (p.13, lines 12-25)

# The first sentence of the conclusions should refer to the effects related specifically to the hourly differences in air pollution.

Reply:

Thank you for your suggestion. We amended the conclusion as follows:

“This study provides further evidence that hourly changes in air pollution exposure increase the risks of respiratory disease,....” (in the Abstract)

“The present study provides further evidence that hourly changes in air pollution exposure increase the risks of respiratory disease.” (p.15, line 14-15)

# again in the conclusions, the sentence about the possible contribution of the finer timing on the onset of symptoms to better understand the mechanisms of damage that air pollution possibly causes on human health, is not supported enough by the results provided. This sentence could remain in the conclusions on the condition that the authors include a corresponding statement in their hypothesis.

Reply:
Thank you for your suggestion. Following your comment, we added the following sentence in the Background section (p.5, lines 7-11):

“We therefore evaluated the associations between hourly changes in air pollution and the risk of respiratory disease onset in residents of Okayama, Japan, who had visited emergency rooms between January 2006 and December 2010. The findings may provide additional insights into the physiological mechanisms of air pollution health effects.”
Responses to comments from Dr. David Stieb

COMMENT
My earlier comments have been satisfactorily addressed. I have no further comments.

Thank you very much for your thoughtful and valuable comments.

We thank the reviewers again for their helpful comment, which we feel has improved our manuscript. We hope that with these modifications, our paper can now be accepted for publication.

Sincerely,
Takashi Yorifuji MD, PhD, on behalf of all authors