Author's response to reviews

Title: Hourly Differences in Air Pollution and Risk of Respiratory Disease: 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 thoughtful and valuable comments. According to your and other reviewer’s comments, we carefully revised our manuscript. Major modification points are as follows: First, we added more explanation in the Methods section. Second, we further examined the effects of other lags (6 to <12 hours, 12 to <18 hours, 18 to <24 hours, and distributed lags). Third, we added further sensitivity analyses. Finally, we expanded the Discussion section. We believe that these modifications made our revised manuscript more scientifically valid and valuable.

Our responses to your comments are described below in a normal font following your comments in boldface.

MAJOR REVISIONS

Methods

The case-crossover description mixes some basic information about the study design (such as that it uses cases only and that it compares the exposure before events with other exposure periods) with a perhaps excessively summary description of how the authors selected the control periods. This description could even be misleading, as it does not make clear whether the control periods were chosen on other days as they were for the 24-hour periods (the metric used by the authors who introduced the time-stratified approach of case-crossover [Maclure, 1991; Lumley 2000]) or on the same days. For the first hypothesis, the authors should state whether they selected as controls the same six-hour intervals on other days as those on which the case occurred; for the second hypothesis, the control periods would be the six-hour intervals preceding and following the six-hour case period within the same day; this is important in relation to the potential confounding by the circadian pattern of the respiratory outcome the authors studied [Peters 2001]. I suggest that the authors explain these points more clearly. On the other hand, to explore the hourly effects within a whole day, I would suggest that the authors cover different lag periods within the same day, as previous studies have done [e.g. Bhaskaran 2011]: for example 7-12, 13-18, 19-24, rather than analysing 12-hour intervals that overlap the 0-6 period.

Reply:

Thank you for your suggestion. We attempted to explain how we selected the controls more clearly as follows (p.7, lines 18-22):
“we thus selected control periods from the same times on other days, on the same days of the week in the same months and years (e.g., the same six-hour intervals on other days on the same days of the week in the same months and years as those on which the case occurred).”

Furthermore, following your suggestion, we considered different lag periods within the same day rather than analyzing intervals that overlap the 0-6 period (p.8, lines 8-15; Table 3). The elevated odds ratio for the association between SO$_2$ exposure 12 to <18 hours prior to the case event and pneumonia and influenza (OR 1.06, 95% CI: 1.00, 1.12) was consistent with the elevated odds ratios observed in Figure 2.

“We first evaluated the effect of exposure to each pollutant, averaged during eight different periods prior to the case event (i.e., emergency calls) (0 to <6 hours, 6 to <12 hours, 12 to <18 hours, 18 to <24 hours, 0 to <24 hours, 24 to <48 hours, 48 to <72 hours, and 72 to <96 hours), on health outcomes (respiratory disease, pneumonia and influenza, and COPD and allied conditions).”

Misclassification of exposure is, however, more than likely when individual exposure assessment cannot be carried out; it has been shown in a re-analysis of the six-city study that only a buffer no greater than 5 kilometres could provide a reliable approximation of exposure to the individual addresses. Moreover, the authors maintain that no hourly data are missing for any of the pollutants they studied or for temperature and humidity. I take the liberty of declining to believe this, since they were studying a 5-year period and as many as 11 monitoring stations. Maybe the authors mean that the values were all imputed, but if that is the case, I would like to be told how they imputed the missing values among the stations, the days and the hours of the same day. This is particularly important because they analyse hourly differences in exposure and the probability of missing data however sparse and although imputed could affect the estimates more than in 24h periods.

Reply:

Thank you very much for your helpful suggestion. As you suggested, we
meant that the values were all imputed and have no missing on several pollutants. We explained how we imputed the data in the text as follows (p.6, lines 12-19):

“We then calculated city-representative hourly average concentrations of each air pollutant from hourly concentrations at each monitoring station. When hourly concentrations at several monitoring stations were not available, we used hourly concentrations at other stations where the data was available to calculate the city-representative hourly average concentrations. Despite these imputations, we lacked 502 hourly concentrations for ozone (1.15% of eligible hours) and 26 for CO (0.06% of eligible hours) during the study period.”

Regarding exposure misclassification, we provided a sensitivity analysis restricting the subjects who lived in the study area which could be covered by 20-km buffers from each monitoring station and obtained the similar results.

Meteorological factors were entered in the analyses with different dfs, selected apparently a priori. I think the authors should have explained this choice, since the apparent temperature (combining T and H) has been used in many other studies. Moreover, it is not clear whether the spline they used for temperature and humidity in the periods shorter than 24 h had the same degree of freedom as those they used for 24h periods.

Reply:

Thank you for your comment. We added an explanation why we adopted these numbers of dfs and conducted a sensitivity analysis changing the number of dfs, but the results did not change. We also used the same dfs in all analyses (both in the periods shorter than 24 h and 24 h periods) and clearly explained it in the text as follows:

“In all analyses, we adjusted for hourly ambient temperature using a natural spline with 6 degrees of freedom (df), hourly relative humidity with 3 df, and weekly numbers of reported influenza cases aged ≥60 among monitoring medical institutions in the city. We chose the number of df following a previous air pollution study in Japan [22] and because the relationship between temperature or humidity and morbidity is considered non-linear. We used
meteorological data at the time of the case event.” (p.8, lines 1-7)

We also added sentences about a sensitivity analysis as follows:

“Finally, we changed number of dfs for hourly ambient temperature and hourly relative humidity to examine the robustness of the results.” (p.9, lines 10-12)

“Finally, when we adopted different no of dfs (hourly ambient temperature with 8 dfs and hourly relative humidity with 5 dfs), the results did not change (data not shown).” (p.11, lines 18-20)

No rationale has been given by the authors for having selected over-65-year-olds, when important effects of air pollutants have been reported, in the scientific literature, for children and adolescents.

Reply:

Thank you for your suggestion. We focused on the elderly a priori because they are considered to be at greater risk of adverse effects. Following your advice, we added a sentence why we focused on the elderly (p.5, lines 21-23):

“We focused on the elderly because they are considered to be at greater risk of the adverse health effects of outdoor air pollution [2].”

The authors studied respiratory outcomes (all, COPD, pneumonia and influenza). They also used medical histories for information about comorbidities, so as to analyse their possible role as effect modifiers. Many questions arise about the health data. The first has to do with their source of information. The outcome of the studied association is defined (in Background, p. 5) as the risk of respiratory disease onset in residents who made ER visits. However, the analysed data refer to people who got to hospital by ambulance, which could have introduced a selection that excluded people who arrived for emergency services by their own means.

Reply:

As you pointed out, we could not include patients who arrived at hospitals by their own means. We consider that this is an issue of generalizability. Following your comment, we added the following paragraph in the Discussion
section (p.14, lines 22-24):

“Finally, we did not include patients who arrived at hospitals by their private vehicles. Therefore, we might not be able to generalize the present findings to all emergency hospital visits.”

Moreover, we do not know if the diagnosis the authors used was made in the emergency room or by “physicians at the hospital” (as is stated in Methods, p. 6), which could mean during a hospitalisation. This point could affect diagnosis reliability, since there would be a difference between those who made only the an ER visit and those who received a hospital diagnosis, or it could bring about another selection of people, if only those hospitalised following their ER visit and for whom a hospital diagnosis was made, were included.

Reply:

Thank you for your comment. Mostly, the diagnosis was made by physicians at the emergency rooms of the hospitals. We confirmed this asking the representative of Ambulance Division of the Fire Bureau in the city of Okayama. We amended the sentences as follows:

“The type of disease was diagnosed by physicians at the emergency rooms of the hospitals to which the patients were transported.” (p.5, line 24-p.6, line 1)

“The type of disease was diagnosed by medical doctors at the emergency rooms of the hospitals to which the patients were transported….”(p.7, lines 4-6)

Another problem concerns influenza: we read that influenza was used, together with pneumonia, as a possible outcome of exposure; yet again these data were not obtained from ER, visits, but instead from public health surveillance. If this is the case, I wonder whether the dual source could have given rise to a non-comparability of the two groups: cases of influenza treated at home and included in the surveillance and cases of other diseases, and even influenza, who have recourse to emergency rooms. I also wonder how the time of onset was assessed for the influenza cases who did not get ERV, and why the authors assume that air pollutants could induce influenza; while pneumonia could be the result of an irritation due to chemical substances (especially gases), respiratory infections
are more likely to be a consequence of environmental exposure at an early age, especially in asthmatic children. Finally, if the diagnoses of comorbidity came from ER, how confident are the authors about the reliability and completeness of this information? Now, a sensitivity analysis could resolve the first point as well as the last by analysing pneumonia without influenza. However, the source of the diagnosis and the time of influenza onset require a clearer definition. Incidentally, I have assumed that “onset” refers to respiratory symptoms or syndromes and not to incident diseases.

Reply:

Thank you for your comment. The diagnosis of the patients in the present study (e.g., the health outcome of “pneumonia and influenza”) was made at the emergency room; thus, the diagnosis of influenza was made at the emergency room where the patients were transferred. (Usually, it takes less than 10 minutes to diagnose influenza in Japan.) The variable of weekly number of reported influenza cases we adjusted in the model was obtained from the public health center. Thus, the two data were from different sources. We apologize for the confusion. We understand your concern whether air pollution could induce influenza infection. Following your comment, we excluded influenza cases in a sensitivity analysis and found that the results did not change substantially. (Only 111 influenza cases were included in the health outcome of “pneumonia and influenza”.) We added sentences regarding sensitivity analysis as follows:

“We also excluded influenza cases from the health outcome of pneumonia and influenza and repeated the analysis.” (p.9, lines 9-10)

“Moreover, when we excluded influenza cases (n=111) from the analysis, OR for pneumonia and influenza was 1.06 (95% CI: 1.00, 1.14) for SO\textsubscript{2} exposure 0 to <24 hours prior to the case events.” (p.11, lines 15-18)

Regarding comorbidity, we added a sentence to explain how the information was collected. We also confirmed it with the representative of the Ambulance Division of the Fire Bureau in the city of Okayama and they consider that the information is reliable and almost complete because they need to show the information for physicians at the emergency rooms of the hospitals.
“The information on comorbidity was obtained from the patients themselves or their relatives by ambulance personnel.” (p.9, lines 2-3)

**Results**

health data Table 1 should report data relative to possible selections of participants as well as the number of patients with no previous diseases and of those for whom information about previous diseases was not available. It seems surprising that only 11% of respiratory diagnoses refer to COPD (the authors also include asthma) in this older population, when COPD emergency hospitalisations generally show values ranging from 25% - 30%. Could the authors check this datum?

**Reply:**

Following your comment, we added more information on comorbidity in Table 1. We also double-checked the percentage of COPD, and found it was correct. As you suggested, it may be related with the fact that we could not include patients who arrived at hospitals by their own means. Therefore, we added the following sentences in the Discussion section (p.13, lines 1-5):

> “Compared to respiratory disease or pneumonia and influenza, the findings for COPD and allied conditions were equivocal, which is inconsistent with the previous studies [2]. This is probably due to small number of cases in the present study. Because we could not include patients who arrived at hospitals by their private vehicles, this may reduce the number of the COPD cases in the present study.”

environmental data Table 2 shows a very high standard deviation for the mean hourly values of pollutants, which in turn causes high IQR for all the pollutants. I suggest that the authors stratify these values into three or four daily time periods, to see how hourly pollutant levels change at different periods of the day (for example: morning, afternoon, night), which would seem to support the advisability of exploring different lags (as I proposed above) or of stratifying the analysis according to different periods of the day. The correlation coefficients (CC) are also lower than those found in earlier studies, especially for SPM and NO2. A recent review found CC between NO2 and PM10 ranging between 0.5-0.9 and CC up to 0.88 between NO2 and PM2.5. I actually remember a recent study from Japan [Katanoda 2011] that reports a CC as low as 0.3 between NO2 and PM2.5,
although for annual data. Have the authors an interpretation for this?

**Reply:**

Following your comment, we stratified the mean concentrations of pollutants into three or four periods, but the trends were similar when we stratified them into two periods (i.e., daytime vs. nighttime) which we adopted in the analysis in Table 4 (effect modification). Therefore, consistent with Table 4, we show the mean concentrations stratified by the two periods in Table 1 and added the following sentence in the Results section (p.9, lines 24 – 25):

“The concentrations for SPM, SO₂, and ozone were higher in the daytime, while concentrations for NO₂ was higher in the nighttime.”

The reason why we did not observe strong correlation between SPM and NO₂ in the present study may also be related with this fact.

**Discussion**

My first general comment concerns a pair of important omissions: the authors do not discuss the negative results and especially how the analytical methods could have affected the results. For example, most studies in a recent review (Bentayeb 2012) of air pollution and respiratory hospitalisations in the elderly, reported important effects on COPD, but the authors apparently did not observe any. On the other hand, many ill-defined steps in carrying out the analyses could have influenced their results, such as the possible misclassification of exposure, the possible selection of patients and choosing to analyse the shorter periods within a day.

**Reply:**

Thank you for your helpful suggestion. Following your suggestion, we added the following paragraph in the Discussion section (p.13, lines 1-5):

“Compared to respiratory disease or pneumonia and influenza, the findings for COPD and allied conditions were equivocal, which is inconsistent with the previous studies [2]. This is probably due to small number of cases in the present study. Because we could not include patients who arrived at hospitals by their private vehicles, this may reduce the number of the COPD cases in the
present study.”

We also attempted to amend the description of limitations of the present study more clearly following your comments.

**Secondly, the references are sometimes dated.**

**Reply:**

We updated and added the following references:


**Coming to more specific comments,**

- although it is possible to agree that working on hourly pollution data and using individual information are among the strengths of this study, I cannot agree that this is the only study that has found effects on acute respiratory events. I suggest that the authors check more recent references than the 1st and 2nd on their list and that they avoid ambiguity between new respiratory events and incident respiratory diseases. Moreover, though most previous studies deal with a daily metric of short-term effects, others use an hourly metric and, by comparing them this study does not support the idea that the authors have here introduced an exact temporal definition: indeed the authors list not having the exact times of disease onset among the limitations of their study.

**Reply:**

Thank you for your suggestion. Following your suggestion, we updated the references and mentioned that the disease onset in the present study may only
refer to appearance of respiratory symptoms as a limitation (p.14, lines 2-10).

“Second, because we did not have the exact times of disease onsets, we used the time of emergency call as the disease onset for each case. Compared with cardiovascular disease, the disease onset of respiratory disease would be difficult to identify and the disease progression is probably gradual. Thus, the disease onset may only indicate the appearance of respiratory symptoms rather than incidence of disease. The present finding that shorter lag for SO\textsubscript{2} than for SPM or ozone may just show the differences in latent periods [36] between disease onset and the need for emergency call, i.e., the different speed in disease progression of the disease which these air pollutants may induce.”

- The authors actually do discuss the possible misclassification of diagnosis. However their comments risk being misleading, since they refer the problem to the diagnostic ability (which could in fact be assumed to be higher in larger hospitals) of the emergency departments, but differential misclassification relates to a systematic difference of diagnosis between exposed and unexposed subjects. On the other hand, even if misclassification is rare, it does not depend on diagnostic ability, but instead on the difference in diagnostic protocols between the emergency room and the wards.

Reply:

As remarked above, the diagnosis was made at emergency rooms. Thus, diagnostic ability is considered similar among patients. Following your comment, we omitted the phrase regarding non-differential disease misclassification in the present revision.

- The Berkson bias is inappropriately cited, since it should properly refer to the possibility that both those exposed to risk and those suffering from respiratory symptoms have recourse independently to emergency room visits, whereas the authors are discussing the different impacts that random and systematic errors cause on estimates.

Reply:

We agree that Berkson bias is inappropriate here. Rather, we aimed to explain our interpretation about measurement error by using another term
“Berkson error”. However, following your comments, we omitted the sentence about Berkson error.

In conclusion, I think the authors should produce a carefully revised version so that the manuscript can be reconsidered for publication.

Reply:
Thank you very much for your valuable comments. We believe that your comments improved our manuscript.
Responses to comments from Dr. David Stieb

Thank you very much for your positive evaluation of our manuscript and your thoughtful and valuable comments. According to your and other reviewer’s comments, we carefully revised our manuscript. Major modification points are as follows: First, we added more explanation in the Methods section. Second, we further examined the effects of other lags (6 to <12 hours, 12 to <18 hours, 18 to <24 hours, and distributed lags). Third, we added further sensitivity analyses. Finally, we expanded the Discussion section. We believe that these modifications made our revised manuscript more scientifically valid and valuable.

Our responses to your comments are described below in a normal font following your comments in boldface.

This is a well written paper describing a case-crossover study of air pollution and ambulance calls for respiratory conditions among the elderly. The methodology appears to be sound and the paper adds to the literature by considering associations on an hourly rather than daily time scale which has been employed in most other studies.

Major compulsory revisions:
1. Most of the reported associations are not statistically significant. The authors should acknowledge that because of the large number of hypothesis tests, the small number of significant associations could be due to chance alone, or provide a rationale for why they believe this is not the case. Their hypothesis might also be more efficiently addressed employing a distributed lag model.

Reply:

Thank you for your suggestion. Following your suggestion, we added the following paragraph in the Discussion section (p.13, line 24 – p.14, line 1):

“However, several limitations should be noted. First, most of the reported associations were not statistically significant. Because of the large number of tests we conducted, there is a possibility of chance findings.”

We also employed a distributed lag model (lag 0 – 3) and found that the ORs for respiratory disease were also elevated for both SPM and ozone exposures. We
added the following sentences and showed the results in Table 3.

“In addition, we applied quadratic distributed lag models to estimate the cumulative effects of the current and the 3 previous days (i.e., <96 hours before) (lags 0–3 days) instead of applying single lag models [24].” (p.8, lines 12-15)

“The point estimates from distributed lag models were also elevated for both exposures.” (p.10, lines 10-11)

2. The weekly number of influenza cases is included as a covariate, while it is also an outcome variable in the pneumonia and influenza models. Consensus is lacking on whether it is necessary to control for influenza epidemics in studies of short term associations with air pollution. In this case, it would be reasonable at least to conduct a sensitivity analysis without weekly influenza cases as a covariate.

Reply:
Thank you for your advice. Following your comment, we conducted a sensitivity analysis without adjusting for weekly numbers of reported influenza cases, and found that the results did not change:

“In addition, we repeated the analyses without adjusting for weekly numbers of reported influenza cases.” (p.9, lines 8-9)

“Not adjusting for weekly numbers of reported influenza cases also provided similar results (data not shown).” (p.11, lines 14-15)

Minor essential revisions:
3. Although a previous paper is cited regarding the basis for number of df in natural splines for temperature and humidity, the authors should still provide a brief explanation.

Reply:
Thank you for your comment. We added a brief explanation why we adopted these numbers of dfs. We also conducted a sensitivity analysis changing the number of dfs, and found that the results did not change:
“We chose the number of df following a previous air pollution study in Japan [22] and because the relationship between temperature or humidity and morbidity is considered non-linear.” (p.8, lines 4-6)

“Finally, we changed number of dfs for hourly ambient temperature and hourly relative humidity to examine the robustness of the results.” (p.9, lines 10-12)

“Finally, when we adopted different no of dfs (hourly ambient temperature with 8 dfs and hourly relative humidity with 5 dfs), the results did not change (data not shown).” (p.11, lines 18-20)

4. In table 1, influenza and pneumonia together account for just over 50% of visits. It would be helpful to include percentage figures other specific conditions accounting for the remaining 40+ percent of visits.

Reply:

Following your suggestion, we added other types of respiratory disease in Table 1.

Discretionary revisions:
5. Consider moving the description of city (population etc.) to the beginning of the data section.

Reply:

Following your suggestion, we moved the description of the study subjects to the beginning of the Methods section.

6. There is considerable experimental evidence that high levels of SO2 cause adverse respiratory effects with a very short time lag (see WHO 2005 Air Quality Guidelines: http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf?ua=1), which could be considered consistent with their observation that SO2 exhibited associations on a shorter time-scale. The authors should consider citing this.

Reply:
Thank you for your suggestion. Following your comment, we added a citation to the website.

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