Author's response to reviews

Title: A Multi-city Time-series Analysis of Air Pollution and Emergency Department Visits for Cardiac and Respiratory Conditions

Authors:

David M Stieb (dave_stieb@hc-sc.gc.ca)
Mieczyslaw Szyszkowicz (mietek_szyszkowicz@hc-sc.gc.ca)
Brian H Rowe (brian.rowe@ualberta.ca)
Judith A Leech (jleech@ottawahospital.on.ca)

Version: 2 **Date:** 14 April 2009

Author's response to reviews:

April 15, 2009

Drs. Philippe Grandjean and David Ozonoff

Editors in Chief

Environmental Health

Dear Drs. Grandjean and Ozonoff

Please find enclosed our revised manuscript, "A multi-city time-series analysis of air pollution and emergency department visits for cardiac and respiratory conditions".

We would like to thank the reviewers for their helpful comments. We address these in an itemized manner below, and where appropriate have made changes to the manuscript. We have also addressed editorial comments.

Sincerely,

David M Stieb, MD, MSc, FRCPC

Population Studies Division

Healthy Environments & Consumer Safety Branch

Health Canada

269 Laurier Ave. W.

3rd Floor, 3-029 PL4903c

Ottawa, Ontario K1A 0K9 (mail) K1P 5J9 (courier)

Phone: (613) 957-3132, Fax: (613) 948-8482

dave_stieb@hc-sc.gc.ca

Itemized response to peer reviewer comments

Reviewer: Bin Jalaludin

1. It would be useful to make some comments on the correlation among air pollutants especially when the authors do present the results from two pollutant models.

Correlations among pollutants are presented by city in a new supplementary file and a brief commentary is provided in the results section of the text.

2. The authors should define summer and winter months.

We have added text to this effect in the methods section.

3. Although the authors have adjusted for seasonal variations, it would be useful for the authors to describe whether this would have also adjusted for influenza and other respiratory disease outbreaks.

We did not adjust for influenza epidemics, although influenza and pneumonia were included in the respiratory infections diagnosis group, and these did not exhibit an association with air pollution. Previous analyses have indicated that these do not affect the association between air pollution and mortality, which prompted the APHENA investigators not to employ additional controls for these variables. (Braga, A; Zanobetti, A. Do respiratory epidemics confound the association between air pollution and daily deaths? Eur Respir J. 2000;16:723–726; Touloumi, G; Samoli, E; Quenel, P; Paldy, A; Anderson, RH; Zmirou, D, et al. Short-term effects of air pollution on total and cardiovascular mortality: the confounding effect of influenza epidemics. Epidemiology. 2005;16:49–57.)

Reviewer: Jennifer Peel

• Methods: Many details are missing from the Methods section. For example, how many pollution monitors are available for each city? What is the geographic size of each city (a map may help here)? What temporal resolution is available for the pollutants (hourly, daily, etc.)? How do you handle missing data? What years are included in the study?

We have added supplementary files which provide the number of monitors for each pollutant as well as the surface area (in square kilometers) of each city. We have added statements in the methods section indicating that all pollutants were measured hourly and that missing data were not imputed. The years covered in each city are provided in table 1.

• Methods, ED visits: Were all ED visits included? Or just residents of a geographic area? What years were included? How did you handle repeat visits (e.g., repeat visits by a single person within the same day or week)?

We have added statements to the methods section indicating that all ED visits were included (i.e. the analysis was not restricted to residents of a geographic area). The years covered in each city are provided in table 1. Repeat visits were not accounted for in the analysis. Previous analyses of data at one site indicated that the incidence of repeat visits within 14 days was less than 10% for all conditions (Stieb DM., Beveridge RC, Smith-Doiron M, Burnett RT, Judek S, Dales RE, Anis AH: Beyond administrative data: characterizing cardiorespiratory disease episodes among patients visiting the emergency department. Can J Public Health 2000, 91:107-112) and exclusion of repeat visits did not have an impact on the results (Stieb DM, Burnett RT, Beveridge RC, Brook JR: Ozone and asthma emergency department visits in Saint John, New Brunswick, Canada. Environ Health Perspect 1996, 104:1354-1360). We therefore did not feel that this issue needed to be pursued further.

• Methods: Do correlations among the pollutants.

Correlations among the pollutants are provided as a new supplementary file and these are discussed briefly in the results section.

• Methods: The AIC and other tests do not evaluate confounding. Why were these used?

Minimization of the AIC was used as a goodness of fit measure to determine the optimal number of knots in the natural spline smoothing functions of time, and the Bartlett's test as a test for white noise. We have clarified this in the methods section.

• Methods: Sensitivity analyses should be performed for all associations, not just those that there statistically significant (so the authors can get a better sense of the effect of the sensitivity analyses).

We see our approach as an efficient way to deal with the large number of combinations of pollutants, outcomes and cities under consideration. We believe we have appropriately focused the sensitivity analyses on the most consistent associations. The observed lack of sensitivity confirms that our primary findings are not spurious.

• Methods: In the various lag models, did you match the lag for meteorologic variables with the lag used for pollution? This is generally preferred.

As indicated in the methods section, we conservatively included meteorological variables with lags of 0, 1 and 2 days.

• Methods: Do you ever present information about how many knots for time are in each model (the final model)? The number of knots in the sensitivity analyses seem to be very high compared to other published studies (e.g., 4 knots per year or 12 knots per year is typical).

We have added a supplementary file indicating the number of knots in the base model. We selected the number of knots per year in the sensitivity analysis to be consistent with and/or bracket those used in other recent studies. In the APHENA study, for instance, 3, 8, and 12 knots per year were employed in the sensitivity analysis.

• Why did you choose to use the daily average for pollutants? Many previous studies have examined 1-hour max or 8-hour max, particularly for gaseous pollutants.

In our experience, 24-hour average pollutant concentrations tend to be highly correlated with one hour or eight hour maximum concentrations, as are the results of regression analyses for these metrics. As indicated in the results section, we did in fact conduct sensitivity analyses using eight hour maximum concentrations for ozone, since this is commonly the form of air quality standards for ozone, and results tended to be similar to but slightly weaker than those based on 24-hour average concentrations.

• Methods: Is the method used for combining city-specific results typical? How does this compare to what NMMAPS or APHENA or similar multi-city studies have used?

The method used for combining results across cities is consistent with that employed in the NMMAPS, APHENA, APHEA and other similar multi-city studies and meta-analyses.

• Method: Why did you choose to examine the individual lags 0-2? A moving average or distributed lag model would have been easier to interpret. As it reads now, there are numerous statistical tests and the statistically significant results are emphasized. This method has been shown to be biased. It seems that you could have narrowed down the amount of tests by using previous literature. For example, many studies have shown that cardiovascular events often have a short lag period. Some respiratory outcomes (e.g., asthma) have been observed to have a longer lag structure with pollution. One approach is to pick a primary lag structure, and then do secondary analyses to evaluate that choice.

There have been relatively few studies examining the association between air pollution and emergency department visits, making it difficult to reach a priori conclusions about probable lags between exposure and effect. Of recent studies cited here, there was no particularly striking pattern in terms of predominant lag effects. We felt it was therefore appropriate to examine individual lags in order to evaluate this issue more fully.

• Results: It would be helpful to be able to see the sub-daily results. Could these be placed in an online supplement?

We have added a supplementary file with results from the sub-daily analyses.

• Discussion: What have other studies observed with regard to seasonal (warm vs. cold) analyses?

Of recent studies cited here, no particular pattern was observed in terms of effect modification by season. As study locations varied widely (Australia, South America, Western Europe, southern and northeastern US), one might not expect to find consistent seasonal patterns.

• Table 1: Provide more descriptive statistics (it may need to be in more than one table) – e.g., standard deviation, IQR. What were the percent of days with data for the gaseous pollutants?

This has been added as a supplementary file.

• It seems that some cities should not have been included for certain pollutants (e.g., Ottawa with 11% and 31% of PM10 and PM2.5 data).

Given the inverse variance weighting procedure we employed to pool results among cities, results from centres with many missing observations would tend not to contribute significantly to pooled results. We therefore do not believe it is necessary to remove this centre from the analysis.

• Table 2: provide the average daily number of visits and the standard deviation (more percentiles would be helpful, too).

These have been added.

Minor Essential Revisions

• Abstract: Add in some information about the time period of the study

We have added a statement to this effect.

• Throughout the manuscript (starting in the abstract), you need to clarify the comparison group when making statements that an estimate is x-fold larger (larger than what?). It is not always clear.

We have corrected this in the abstract, but could not find any other instances in the manuscript where the comparison was not clear.

• Background, page 4: The percent of ED visits that are hospitalized would vary by condition, correct? Is it not much higher for CVD visits?

The reference we cite here provides the percentage of ED visits which resulted in a hospital admission, by condition. This ranged from less than 10% for asthma to over 40% for cardiac conditions.

• Methods: Provide reference for EPA methods.

A reference has been added.

• Background: More and more relevant references should be included in the first sentence (no references are currently provided for hospital admissions): e.g., large multi-city studies (NMMAPS, APHENA), review articles, etc.

References have been added.

• Methods: How was the unit increase in pollution used for results chosen? Is it the mean? Typically studies use the IQR.

As stated in the final sentence of the methods section and in the third column of tables 3 and 4, percent increases in visits were expressed in relation to the mean pollutant concentration. Past studies have expressed results in various ways including in relation to the mean (perhaps most commonly), but also in relation to the inter-quartile range and in some cases based on fixed increments such as 10 ppb. We believe that expressing results relative to the mean or interquartile arrange is preferred because the impact of each pollutant can then be compared on an equal basis. In this regard, the mean and interquartile range are equivalent, so we prefer to simply leave our results in their current form.

• Results: Can you provide more details about the missing data? E.g., are there any patterns to the missing data (e.g., certain seasons)? Is ozone measured year-round?

Continuous PM monitors were in the process of being introduced in the late 1990s at most sites meaning that data were often missing early in the time-series. We had added a statement to this effect in the methods section. Ozone was measured year-round.

• Results, page 12: provide 95% confidence intervals rather than p-values.

We have added 95% confidence intervals.

• Discussion: There is an updated publication for the Atlanta ED study (Tolbert et al., JESEE, 2007).

We have added this reference.

• Discussion: The statement about the false positive results in misleading. Performing numerous statistical tests does not change the probability of false positive results (the alpha level is set), but you may see more of the false positive results (i.e., if you do 100 tests you would expect to see 5 statistically significant results and if you do 1000 tests you would expect 50, but the probability is the same).

We have edited the text, so that it now refers to the expected number of false positive results, rather than their probability.

• Discussion: The negative results are not discussed much. The results for some of the smaller outcomes are largely negative (not necessarily statistically significant for the smaller outcomes). Are there other reasons for this (other than chance)? Perhaps the control of temporal trends? Inverse correlations with other pollutants? Are these consistent across seasons?

We did not note any particular patterns of negative and non-statistically significant results (or for that matter positive and non-statistically significant results) that would warrant discussion. We believe this would be overly speculative and that we have appropriately focused our attention on those results which exhibited the greatest consistency.

Discretionary Revisions

• The term “weather” is not very technically specific. “Meteorologic factors” is generally preferred by atmospheric scientists.

We see the terms "weather" and "meteorologic factors" as being equivalent for our purposes and prefer to leave this as is. In any case, we do specify the precise variables i.e. temperature and humidity which we use in our analysis.

• Discussion, first sentence: the term “significance” should be reserved for statistical significance. Consider using another term, such as “important.”

We do not see our use of the term as problematic, since we are in fact referring to results which were statistically significant.

• Abbreviation NAPS is probably not needed.

We prefer to leave this in the list for completeness.