Subject: BMJ - Decision on Manuscript ID BMJ-2018-048424

Body: 18-Apr-2019

Dear Mr. Wei,

Manuscript ID BMJ-2018-048424 entitled "Air pollution and cause-specific risks and costs of hospital admissions"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. 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.. We are looking forward to reading the revised version and reaching a final 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.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Sincerely,
Elizabeth Loder, MD, MPH
eloder@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.

Present: Wim Weber (chair); Tim Cole (statistician); Elizabeth Loder; Helen MacDonald; Tiago Villanueva

Decision: Put points. Statistician will review revision.

* The outcomes of hospitalizations, death and other clinical outcomes are important and generalizable. The economic outcomes are less relevant for a non-US audience. They do not detract from the value of the paper but may be less relevant.

- Our statistician thought the analysis was broadly valid but would like the following points addressed in a revision:

-Reduce the emphasis on statistical significance, given that n = 95 million.

*-What this study adds, item 2, this seems confirmatory not new.

- Please explain more clearly why the focus is on PM2.5 rather than say PM5 or PM10.

-How focussed is a zip code for estimating exposure to PM2.5?

-Odd that the analysis focuses on the health improvement due to reducing PM2.5 rather than the more obvious health risk of PM2.5, i.e. inverting all the risk ratios. Ref 3 points out this is causal language – risk reduction. We agree.

-Page 10 lists five distinct outcomes: hospitalizations, in-hospital deaths (not deaths at discharge), discharges to nursing homes and to home, plus days of hospitalization. But actually they are all the same – i.e. outcome 1 suitably scaled to reflect the average experience. Thus they are all significant to the same extent. This assumes for example that PM2.5 does not affect the proportion of deaths among hospitalizations, which is a strong assumption and easily tested by modelling in-hospital deaths as a separate outcome. And ditto for "outcomes" 3 to 5.

* We thought that the PM2.5 exposure measurements are not explained well: you say you used zip codes and then go on to "estimate daily PM2.5 levels with a 1 km × 1 km resolution in the continental US using a well-validated satellite-based neural network model". At what level did you input the PM2.5 exposure per patient ?

* Consider providing a bit more information in the introduction about the various types of particulate matter, where they come from, known health problems linked to them.

* In the methods would help to say in plain english what a "disease group"

* Missing both PPI declaration and dissemination plan. This is where authors could potentially involve patients and advocacy groups by preparing with then materials for advocacy groups, presenting with them about the issues etc.

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.

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

Comments:
This is an interesting and informative study which is of interest for both policy and academic communities (public health, health economics). The study utilises a large database (Medicare records) to assess risk of hospitalisation associated with PM2.5 exposure for specific disease groups among the elderly US population. The links between short-term PM2.5 exposure and increased risk of hospital admission for respiratory and cardiovascular disease are well established; however this study extends current understanding to a wide range of disease conditions, and estimates the associated economic burden.

The methodology applied is not novel, however the use of a large scale database of a vulnerable population group and case-crossover design is a suitable approach, generating findings which contributes to existing knowledge in this context (US).

Title and abstract
- The title does not clearly reflect the setting of the study or the study population and would be more accurate if it referred to elderly Medicare recipients.

Introduction:
- The authors do not explicitly outline the rationale for selection of patients aged >65 years) and further detail concerning the vulnerabilities of this group would be helpful.
- The use of the term 'agnostic' is unusual and presumably refers to a null a priori hypothesis and objective research approach. This could be improved by use of an alternative term.
- Classification of disease outcomes into 214 mutually exclusive groups is not adequately justified. Many of these conditions will have overlapping and interrelated aetiological and risk factors which is overlooked by the study authors.
- The Medicare population is unlikely to be representative of the general population, therefore the study has an inherent selection bias. The implications of the use of this database merit further consideration and exploration in the background text.

Methods:
- The study time period (2000-2012) is not described in sufficient detail and it is unclear why more recent data was not included in the study. Demographic (and air pollutant composition) changes since 2000 limit interpretation and generalisability of study findings.
- Provision of informal care (e.g. by family members) and associated opportunity costs has not been considered or costed within health economic analyses (presumably due to the limitations of data sources used).
- PM2.5 exposure data are modelled from US EPA monitoring station data, however these estimates will be less reliable in rural areas with lower background concentrations. There is no reference to the lack of information concerning indoor and occupational exposures.
- The study is reliant upon accurate coding of hospital admissions and this process requires further detailed description.
- Seasonal factors will be associated with both pollutant concentrations and risk of hospital admission and therefore merit consideration in the analyses.
Discussion
- This could be improved with a more detailed consideration of the limitations concerning generalisability of study findings, given the characteristics of the study population.
- Behavioural factors are important confounding factors which are not considered – these are also likely to influence and modify a range of risk factors. High pollutant episodes may also result in changes in medication regimens for those with chronic conditions, which in turn could increase hospitalisation risk. The discussion does not adequately capture the complexity of these relationships and implies a causal relationship between short-term PM2.5 concentrations and risk of hospitalisation for a wide range of disease outcomes.

Additional Questions:
Please enter your name: Dr Suzanne Bartington

Job Title: Clinical Research Fellow

Institution: University of Birmingham

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 2

Comments:
Wei et al. reported the results of one of the largest case-crossover studies ever conducted to investigate the potential health and economic implications of short-term PM_{2.5} exposure, based on 12 years of Medicare inpatient hospital claims data from the United States. While the short-term association of PM_{2.5} and a range of cardio-respiratory diseases have been extensively studied, the present study undertook an agnostic approach to look at 214 mutually exclusive categories of diseases covering nearly all plausible disease conditions. It is an interesting study, but there are several aspects of the manuscript where considerable revisions could be useful before it is considered for publication.

Some fundamental issues:
• The use of causal language: as an observational study, this manuscript was written, rather inappropriately, in a causal tone. The authors reported relative/ absolute risk or cost "reduction" associated with per unit "reduction" of exposure as if intervention was conducted to alter PM_{2.5} levels. Similarly, the claims on economic "benefits" associated with PM_{2.5} "reduction" also inappropriately imply causality (for the sake of consistency, I will use the term "cost" instead of "benefit" from this point onward).

It would be more appropriate to present at least the main results the other way round, to show the excess risks and costs of hospitalisation associated with higher PM_{2.5}, and avoid using causal language (e.g. "reduction") throughout the manuscript.

• The use of an agnostic approach: this approach could be valuable, especially for generating hypothesis. However, because of the use of causal language, the results/ discussions on the newly identified associations do not appropriately reflect that this study is generating new hypothesis for those conditions and the totality of evidence for those are relatively weak.

It is important to indicate which of the disease conditions were rarely studied on the tables and figures (in addition to the in-text descriptions on some of those conditions), to help readers who are not familiar with the literature to evaluate the evidence appropriately.

In the discussion section, the authors attempted to explain some of the novel associations observed by linking various different conditions which have been suggested (not always with

abundant evidence) to be linked to PM_{2.5}. These were highly speculative and they provided no data from their study to support their claims. Taking a similar approach, one could argue that increased PM_{2.5} exposure is linked to angina/ shortness of breath/ COPD exacerbation, which may in turn link to injuries (e.g. fall/ traffic accident/ suffocation), which are part of the negative controls of this study. I believe a better approach would be to acknowledge the lack of existing evidence (and novelty) on those associations and call for further investigations into the mechanisms/ epidemiological associations directly.

• Estimation of healthcare costs/ benefits: the estimated healthcare costs may be subject to bias, because a substantial fraction of that came from weak statistical associations that are not adequately supported by literature. I agree with the authors that the previous estimations based on several major cardio-respiratory diseases could be underestimating the total costs, but they should also acknowledge the potential bias by the novel associations (e.g. not causally linked conditions i.e. false positive) / agnostic approach (underestimation: e.g. null association for some conditions e.g. stroke that would have been included in the previous estimation).

For the above reasons, reporting overall summary estimates for cost/ hospital admission could be very misleading. I suggest the authors to present the aggregated absolute numbers of hospitalisation and costs related to the more well-established conditions (e.g. cardiorespiratory disease) and those related to the novel ones separately, and note more clearly that the latter ones are of greater uncertainty.

• Disease classification: I am not sure whether examining the 214 disease conditions separately is the ideal approach to maximise the utility of the data. Many of the conditions (e.g. some of the cardiovascular diseases) are closely related and share similar disease pathogenesis pathways, and they are often studied together in broader categories in relevant literature (including clinical trials). The separation of these related conditions could be clinically informative for some specialists, given sufficient statistical power, but the present study (despite the enormous sample size) does suffer from the lack of power, especially given after Bonferroni correction as the authors noted. This is especially unhelpful to policymakers who need no overly-scattered information on sub-classes of disease conditions (vs broad categories of major diseases).

Combining related conditions could 1) reduce the number of comparisons made and improve statistical power of the analyses, thus reducing false negatives and enhance the robustness of the results; and 2) provide more comprehensible results for policymakers and epidemiologists.

Other major comments:
• The limitations of the exposure classification method were not adequately discussed:
  o The exposure assessment model is probably one of the best available, but the R-squared vary considerably across the continent, with rather poor validity for some parts of the US, especially central, north and southwest.

  o Although the authors noted that the use of ZIP codes instead of individual addresses may result in misclassification, more elaboration is needed. For example, the geographical coverage of ZIP codes vary substantially and is rather large in general (~90-square miles according to online sources) – that means every single participant (possibly thousands) in the same ZIP code would have identical exposure value.

• Other limitations:
  o I'd love to see some discussion about how changing air pollution levels may influence individuals' health seeking behaviour (not biologically influencing the disease conditions) which may in turn confound the observed association – and this can't be addressed in the present study.

o The confounding effects from lifestyle factors, such as smoking and drinking, may not be fully accounted for by the case-crossover design. Although relatively little literature exist, it is logical to expect that short-term day-to-day variation in e.g. smoking (a form of aerosol exposure) may induce certain health effects if this is true for tiny variations (1μg/m³) of ambient PM_{2.5}. It is unreasonable to expect any study of this kind to be able to fully account for such confounding effects, but one should not just omit that and the results should be interpreted in the light of such limitation.

Minor comments:

• Abstract: It would be helpful to provide not only qualitative summary of the key findings but also the relative risk estimates (and 95% CIs) for each of the outcome mentioned to enable a more immediate understanding about the effect sizes of the associations identified.

• Introduction:

o A brief qualitative definition of particulate matter or PM2.5 would be needed for the general readership of BMJ who may not be familiar with the concept

o The GBD study cited is not up-to-date.

o Please provide relevant references to support the statement about the long-term health effects of PM_{2.5} exposure.

• Statistical analysis:

o As the authors noted, the use of Bonferroni correction could be overly-conservative, and some previously known associations (e.g. with stroke admission) were found to be statistically not significant. I suggest the authors to use false discovery rate adjustment for the main analysis and Bonferroni correction for sensitivity analysis.

o The distributed lag effect of temperature could be well-beyond 5 days (at least for acute cardiovascular and respiratory conditions) and the effects of 1°C change in temperature is larger than, if not similar to, that of 1μg/m³ PM_{2.5}. I am not sure the adjustments for lag 0-1 in the main analyses and lag 0-4 in the sensitivity analyses could account for the confounding adequately. Indeed, some of the results from the sensitivity models tend to be slightly larger than those from the main models (although not statistically significant; e.g. CSS 101). It is also worth noting that the (counter-intuitive) negative association with influenza, for example, became non-significant in the sensitivity model, and temperature is closely linked to upper respiratory infection. Further sensitivity analysis by adopting different distributed lag structure is recommended.

o Why was relative humidity not adjusted for?

o The authors are leading experts in their field, but it may be more appropriate to cite slightly more of others' work in supporting the use of the time-stratified case-crossover analytical approach, as opposed to having 3 out of 4 references being their previous work (page 8 lines 25-30)?

• Disease endpoints specifications: some of the disease categories could be rather vague, especially for non-clinicians. It would be helpful to include a list of the endpoints studied and their corresponding ICD-10 codes (ICD-9 optional) in the appendix – ICD-10 because it can be presented more neatly than ICD-9 and that is what the majority of the world use in the past decade.

• The cumulative excess costs associated with PM_{2.5} exposure appeared to be enormous, but it is important to evaluate this in the light of the total healthcare cost in the US or Medicare system – as it is well-established that the US healthcare system is not the

most efficient one worldwide. Presenting proportion / some form of attributable fraction would be helpful to more objectively evaluate the relative economic burden, and it will be more relatable and comparable to other settings with different healthcare systems.

Additional Questions:
Please enter your name: Ka Hung Chan

Job Title: Research Fellow

Institution: University of Oxford

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

Fees for consulting?: No

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Reviewer: 3

Comments:
This paper assesses the risks of hospitalizations and the healthcare costs associated with short-term exposure to PM2.5.
The authors investigate 214 disease groups and give the number of hospitalizations, the healthcare costs and the value of statistical life for each 1 ug/m3 reduction in PM2.5 exposure.

The originality of the paper is based on the huge number of conditions studied, and on the economic evaluation. Given the number of disease groups, with conditions that have not been investigated in previous studies on short-term effects of air pollution, the paper will encourage future research on the topic. The economic costs reported will provide policymakers important information.

I think that in this moment a paper based on an agnostic approach is useful for both WHO and local governments.

The paper is well described and the methods impeccable. I have a minor comment:

1) Page 5 lines 31-36. "While the health effects of long-term…lacking"
I suggest rephrasing the sentence, because it can be misleading. The diseases were investigated in the two approaches (long and short term) according to specific hypotheses and data availability. However, I think that a comprehensive analysis can be very useful.

Additional Questions:
Please enter your name: Cesaroni Giulia

Job Title: Senior researcher

Institution: Epidemiology Dept. of Lazio Regional Health Service, ASL RM1

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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