Author’s response to reviews

Title: The Impact of Long-Term PM2.5 Exposure on Specific Causes of Death: Exposure-Response Curves and Effect Modification among 53 million U.S. Medicare Beneficiaries

Authors:

Bingyu Wang (rainicy@ccs.neu.edu; rainicy925@gmail.com)
Ki-Do Eum (Ki-Do.Eum@tufts.edu)
Fatemeh Kazemiparkouhi (Fatemeh.Kazemiparkouhi@tufts.edu)
Cheng Li (chengli@ccs.neu.edu)
Justin Manjourides (J.Manjourides@northeastern.edu)
Virgil Pavlu (vip@ccs.neu.edu)
Helen Suh (Helen.Suh@tufts.edu)

Version: 2 Date: 13 Jan 2020

Author’s response to reviews:

We would like to thank the reviewers for their thoughtful comments and efforts towards improving our manuscript. We have made changes to our manuscript to reflect these comments as described below. Note that revisions made in response to reviewer comments are indicated in our manuscript in red font.
Reviewer #1:

The authors revised/added text for the interpretation of previous studies (e.g. Di et al. (2017)), but it makes me confused. In the response letter, the authors said, "Figures 3, S7 and S8 from the Di et al. (2017) paper support our interpretation of their findings. Di et al. (2017) figures show slightly lower associations when PM2.5 exposures were below as compared to above approximately 8 ug/m3, similar to our study." However, in the text, it also said, "our finding of lower non-accidental mortality risks at low PM2.5 levels is contrary to previous studies of Medicare beneficiaries (5, 50), who reported higher and linear all-cause mortality risks at low PM2.5 concentrations." The authors need to clarify this interpretation. The reviewer 2 suggests citing some results from Global Burden of Disease, and I strongly agree with this suggestion. For instance, Cohen et al. (Lancet 2017), found steep exposure-response curve in lower PM2.5 level, which is different from this study. The authors are encouraged to interpret these inconsistent results with potential explanation. I believe this part is one of the most important part of the paper, and the authors had better develop the discussion with caution. As a minor note, the sentence "RRs were non-linear, with lower, but positive and significant, RRs when exposures were lower as compared to higher than 10ug/m3 (Figure 1)" needs to be revised to clarify.

Response:

We have further revised our paper to correct our interpretation of the Di et al. (2017) results:

[Line 172 - 173] “The shape of the exposure-response curve, however, was sub-linear, with lower RRs when PM2.5 exposures were lower than 10 μg/m3 (Figure 1).”

[Line 253 - 258] “Our findings may explain the observed linear or supra-linear associations from previous US, Canadian and western European cohort studies, which were based primarily in urban areas. Note that our findings with regard to the shape of the exposure-response are not comparable to those reported in Cohen et al. (22) in their Global Burden of Disease analysis, which estimated effects of PM2.5 exposure at levels above those observed in US, Canadian, and western European air pollution cohort studies. Thus, the range of exposures examined in Cohen et al. (22) were substantially wider and higher than that in our study.”
“As above, our null (and even significant but protective) RRs for lung cancer and respiratory mortality within rural populations may also reflect confounding by smoking, for which rates are higher in rural populations (29); however, potential confounding of associations between PM2.5 and lung cancer and respiratory mortality by smoking with rural populations has not yet been studied.”

Reviewer #2:
- Line 23: Note phrase "non-combustion" instead of "non-traffic" here

Response:
It has been changed to non-traffic. [Line 22]

- Line 51-53: Somewhat misleading sentence, since Di et al. (reference 5) looks at the exact same population as this study, as do other large-scale administrative databases and other cohorts. Text should ideally parse out the studies that focused on white/urban/higher SES populations, and then those that included more diverse populations with their separable limitations.

Response:
We revised the text as below:

“More recently, studies have expanded their geographic scope through the use of spatio-temporal models to predict exposures for participants living away from air pollution monitoring sites (5,11,12), although most still largely focus on white, urban and higher SES populations (11,12) or on all-cause (5) or CVD-related (13,14) causes of death. Of note, one study of California elderly found higher risks for CVD mortality for rural as compared to urban populations (15).”
- Line 59-61: Similarly, I don't think the authors are making the strongest case here. Many studies have done these things, individually or together (again, Di et al. looked at SES surrogates, race, lower PM, and urban vs. rural populations). The case needs to be made that what the authors are doing here involves novel methods to better elucidate these effects, versus just saying that studies haven't done this.

Response:

We have claimed our contribution:

[Line 60 - 62] “New approaches are needed to examine PM2.5-associated risks of mortality more comprehensively, especially with regards to differentiation of risks for specific causes of death, for potentially susceptible sub-populations, and at low PM2.5 exposures.”

- Line 122-130: This is a greatly improved presentation of the approach. I still think there is some overinterpretation, as the authors could be capturing primary vs. secondary PM rather than traffic vs. non-traffic, but I think this can be handled in the discussion section (though some caveats could be included here as well). It is also worth being explicit, here or elsewhere, that this approach provides the ability to compare non-traffic (or secondary) PM with total PM but does not provide the ability to compare non-traffic with traffic PM. That would help explain why the tables are presented as they are. Alternatively, NO2 could be used as the proxy for traffic PM in the comparison, though that comes with its own interpretation challenges.

Response:

[Line 127-128] “Note that our approach allows us to compare RRs associated with non-traffic PM2.5 to those for total PM2.5 but not to traffic-related PM2.5.”

- Line 141: Number needed before "billion"

Response:

[Line 144] “3.8 billion”
- Line 195-198: The fact that the associations are greatly attenuated for rural populations for lung cancer and respiratory disease (and are even significant but protective) raises questions about the potential role of smoking as a confounder. Smoking rates are clearly higher in rural settings, where air pollution is generally lower. This could contribute to the non-monotonic patterns for lung cancer and these associations. The authors should at least discuss this point. Di et al. did rule out smoking as a potential confounder in their MCBS analysis, but didn't look specifically at this question of urban vs. rural associations.

Response:

Based on the reviewer’s suggestion, we have added the following paragraphs:

[Line 280-284] “Our null finding for respiratory mortality within rural populations raise concerns about potential confounding by smoking. Although Di et al. (5) ruled out smoking as a potential confounder in their sensitivity analysis, their analysis focused only on all-cause mortality and further did not specifically assess confounding by smoking within rural populations, who have higher smoking rates (29) and lower average PM2.5 levels.”

[Line 338 - 341] “As above, our null (and even significant but protective) RRs for lung cancer and respiratory mortality within rural populations may also reflect confounding by smoking (29); however, potential confounding of associations between PM2.5 and lung cancer and respiratory mortality by smoking with rural populations has not yet been studied.”

- Line 210-211: Per above, it could be argued that the residuals are a surrogate of secondarily-generated PM through the correlation with sulfate, not coal specifically (obviously sulfate is an indicator of coal, but in this context could be more of a secondary formation indicator).

Response:

[Line 214 - 215] “suggesting that the residuals may also serve as a surrogate measure for secondary or coal-associated PM2.5.”
- Line 249-250: This conclusion feels like an overreach, given linear or supra-linear associations in studies like CanCHEC or other studies in the Medicare population that included rural populations.

Response:
We added the following text to address this comment:

[Line 253 - 259] “Our findings for urban beneficiaries may explain the observed linear or supra-linear associations from previous US, Canadian and western European cohort studies, which were based primarily in urban areas. Note that our findings with regard to the shape of the exposure-response are not comparable to those reported in Cohen et al. (22) in their Global Burden of Disease analysis, which was intended to estimate effects of a wide range of PM2.5 exposure levels, including those well above that observed in US, Canadian, and western European air pollution cohort studies. Thus, the range of exposures examined in Cohen et al. (22) were substantially higher than that in our study.”

- Line 276-277: This would be a place to potentially talk about the lack of smoking data and the implications, per the discussion above.

Response:

Based on the reviewer’s previous suggestion, we have added the following paragraphs:

[Line 280-284] “Our null finding for respiratory mortality within rural populations raise concerns about potential confounding by smoking. Although Di et al. (5) ruled out smoking as a potential confounder in their sensitivity analysis, their analysis focused only on all-cause mortality and further did not specifically assess confounding by smoking within rural populations, who have higher smoking rates (29) and lower average PM2.5 levels.”

[Line 338 - 341] “As above, our null (and even significant but protective) RRs for lung cancer and respiratory mortality within rural populations may also reflect confounding by smoking (29); however, potential confounding of associations between PM2.5 and lung cancer and respiratory mortality by smoking with rural populations has not yet been studied.”
- Line 293-296: This would be a place to acknowledge that you may have developed surrogates for primary vs. secondary PM, rather than traffic vs. coal.

Response:

[Line 301 - 303] “Alternatively or in addition, our findings may also indicate the importance of primary (but not secondary) PM2.5 as a risk factor for mortality, given the high correlation of non-traffic PM2.5 with sulfate. As a measure of non-traffic and traffic PM2.5-associated risks, however,”

[Line 310 - 313] “which given its high correlation with sulfate, may also serve as a marker for secondary PM2.5 and/or coal-combustion. Differences in our findings likely result from imprecision in estimates of non-traffic PM2.5, as well as differences in our study population and control for confounders.”