Reviewer's report

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

Version: 0 Date: 09 Sep 2019

Reviewer: Jonathan Levy

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General comments

This article involves an investigation of the association between long-term exposure to fine particulate matter and mortality among the Medicare population. Multiple studies have published very similar analyses. The authors themselves published a study looking at the same years in Medicare, but using PM2.5 monitors rather than a gridded model, and therefore with fewer study participants. Other researchers (i.e., Di et al. 2017) published a study looking at Medicare with more years and with a more highly resolved (1 x 1 km) air pollution model. The overarching question is therefore the value added of this study relative to others. From the authors' description, it appears that they believe that the novel elements include the inclusion of populations not living near monitoring sites, the use of code to allow for better use of "big data", examination of cause-specific mortality, and a technique to try to differentiate combustion vs. non-combustion particulate matter. Given the volume of research using similar or identical Medicare and air pollution data, the authors need to more clearly amplify the arguments regarding what is novel and to indicate more precisely the reasons for differences in comparison with other studies. At first glance, many other studies have included populations not near monitoring sites or have examined mortality causes, and the approach to differentiate combustion vs. non-combustion particulate matter has some significant limitations. The novelty would then be mostly related to the novel code implementation, which may not be most relevant to this audience but could have some value. Some reframing of the paper to emphasize what is new in this paper relative to others would strengthen it.
Specific comments

- Lines 41-50: The introductory paragraph reasonably articulates the limitations of some of the literature, honing in on the generalizability of studies that rely on air pollution monitors for exposure characterization. However, there have been many studies published (including Di et al. 2017, citation #5, but not limited to this) that have used pollution surfaces predicted via machine learning and other approaches. The authors should be direct about the fact that these studies exist, and clear about what their limitations are and how the current study advances beyond what was previously done.

- Line 58: It is stated that confounding by nitrogen dioxide is investigated, but that is not entirely correct. If I understand the approach, rather than including nitrogen dioxide in a model with PM2.5, the authors fit models for PM2.5 and then fit models for the residuals after regressing PM2.5 on NO2, as a surrogate for non-combustion PM. That's not the same as examining the impact of confounding by NO2.

- Lines 70-77: With studies having already been published with 1 x 1 km PM2.5, it would be important to articulate the advantage of using this dataset, or at the very least, to argue why there are no strong disadvantages. Obviously this is somewhat about the practicality of which data were accessible by the research team, but some text about comparability of model performance, the fact that coarse resolution could be fine with ZIP code address resolution, etc., would be valuable. Also, the absence of ozone, shown elsewhere to be associated with mortality in this population, should be acknowledged (and ideally addressed).

- Lines 99-102: I find this strategy to determine a surrogate for non-combustion PM a bit puzzling. The argument is that NO2 originates from combustion sources, so the residuals from a regression of PM2.5 on NO2 could be interpreted as non-combustion. But NO2 is predominantly about motor vehicle combustion, whereas there are other sources of combustion (i.e., coal, oil) that include NO2 but could be better proxied by SO2, V, Ni, etc. Plus, PM2.5 is dominated by regional contributions, whereas NO2 is principally local. There could be places with high PM2.5 but low NO2 in rural areas downwind from coal-fired power plants, where concentrations would be combustion-dominated but residuals would be positive. The authors also show no data about the patterns of these residuals to validate this approach versus studies that have looked at speciated PM to better characterize combustion vs. non-combustion sources. If this is to be included, it needs much better justification - calling this non-combustion PM2.5 in the text is definitely a stretch.
- Lines 104-107 and following: This appears to be a potentially interesting statistical innovation, though the strengths and weaknesses of the approach are beyond my expertise (and likely beyond the expertise of many readers of this journal). This may merit its own stand-alone statistical methods paper, or at the very least, more amplified attention in this paper (with corresponding reductions in other sections that do not appear as strong). The authors later argue that these methods avoid limitations in other high-profile papers and that this can lead to different shapes of the exposure-response curves. If the authors can justify these arguments, this is very important.

- Line 145: Since Hispanic status is evaluated distinctly from race, how is the race stratification done?

- Lines 251-255: The text here merits deeper discussion. The authors argue that RRs are lower for below vs. above 10 ug/m3 for non-accidental mortality, when most of the recent literature has shown the opposite. A more detailed discussion about why the authors think their findings are different and what the implications are would be helpful, especially given the policy and public health importance of the finding. In a brief sentence, the authors argue that the differences in comparison with one study are attributable to "their meta-analytic approach which analyzed beneficiaries in groups rather than simultaneously." It's not entirely clear what the authors mean by this or why it would change the shape of the exposure-response function, but it is worth elucidating, and also comparing to other papers that showed comparable curve shapes (i.e., Global Burden of Disease, Liu et al. 2019 NEJM for acute mortality). Is the argument that the literature as a whole has generally used a different method than the authors, and that this can have an influence on the shape of the exposure-response function? Right now, this reads as extremely speculative, so the authors need to bolster the argument if they want to make this case.

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