PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day readmissions in end-stage renal disease patients: population based retrospective cohort study
AUTHORS	Wyatt, Lauren; Xi, Yuzhi; Kshirsagar, Abhijit; Di, Qian; Ward-Caviness, Cavin; Wade, Timothy; Cascio, Wayne E.; Rappold, Ana

VERSION 1 – REVIEW

REVIEWER	Shengzhi Sun Boston University School of Public Health
REVIEW RETURNED	08-Aug-2020

GENERAL COMMENTS	This is a compressive study to examine the association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day readmissions in end-stage renal disease patients. Large sample size is clearly a big advantage. The statistical methods are solid. I only have a few minor comments. 1. The authors used US claim data, and they used conditional Poisson regression to analyze the data. The number of people enrolled healthcare plan could change substantially on a daily basis. The authors please control for the changing population at risk in your models. 2. Instead of assuming the relationship between PM2.5 and hospitalizations is linear, please use splines function to examine the relationship (figure 3) 3. The authors seem missed the following relevant paper: https://doi.org/10.1016/j.chemosphere.2020.125913

REVIEWER	Tazeen Jafar Duke-NUS Singapore
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	The manuscript entitled “Association of short-term exposure to ambient PM2.5 with hospital admission and 30-day readmission in end-stage renal disease patients: population based retrospective cohort study” is a well written manuscript. The topic is interesting, and statistical analyses are well done. However, I have some concerns: 1. My biggest concern is whether high PM2.5 is a proxy for the socially disadvantaged neighborhoods. The association between poorer zip codes with mortality and adverse outcomes is well established in the US. I would encourage the investigators to

	account for neighborhood in the models to determine the independent effect of PM2.5 on the primary outcome. 2. Additional model adjustments – models of admission adjusted for meteorological conditions, while models of readmission included additional patient-specific and hospitalization event-specific variables. Could the authors please explain why the patient-specific and hospitalization event-specific variables were not included in the model for admission? These variables could indicate the general characteristics and overall health of the patient, which could be associated with admission? 3. In addition, both models of admission and models of readmission did not not have direct proxies of patient health other than times of prior hospital admissions, such as years after dialysis, lipid levels, C-reactive protein levels, etc. Are these variables available in the dataset? If not, this shall be mentioned in the limitation sections as potential residual confounding factors. 4. Authors may consider adding a few lines in the discussion on what is the public health implication of the current study.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Shengzhi Sun
Institution and Country: Boston University School of Public Health Competing interests: None declared
Please leave your comments for the authors below This is a compressive study to examine the association of short-term exposure to ambient PM2.5 with hospital admissions and 30-day readmissions
in end-stage renal disease patients. Large sample size is clearly a big advantage. The statistical methods
are solid. I only have a few minor comments.
1. The authors used US claim data, and they used conditional Poisson regression to analyze the data. The
number of people enrolled healthcare plan could change substantially on a daily basis. The authors please control for the changing population at risk in your models.
The reviewer is correct that the number of people enrolled and removed from the health care plan varies on a daily basis. However, the data on total number of enrollees per day was not known for this study. Our study controlled for potential population at risk changes through the modeling structure. The conditional Poisson models create strata by county-month, and day of week to control for potential county differences, including those that may change over time, like the population at risk. We used time stratified design to minimizes the risk of time-related bias. More specifically, in this study design, variation in the population size at risk at scales equal to or larger than a month are controlled for. Including additional controls for population size at risk would have no effect on our results since this denominator would be dropped out of the likelihood which conditions on the variation within a month. We realize that our models may be limited in their control of population risk changes within a 30-day interval and have added this to our limitations section.
2. Instead of assuming the relationship between PM2.5 and hospitalizations is linear, please use splines function to examine the relationship (figure 3)

We agree with the reviewer that the shape of the concentration-response curve is an important consideration. To consider the possibility of a non-linear response with respect to PM2.5, we considered spline models with 3 and 5 degrees of freedom. Models with PM treated as a nonlinear function produced poorer model fit (increased AIC and BIC) and wider confidence intervals around estimates indicating more uncertainty. This result is not surprising and is supported by previous literature that non-linear concentration-response have functions are found only at higher PM2.5 concentrations, whereas our study domain included relatively low concentrations (mean 9.3 µg/m3, SD 5.4 ug/m3) within which range the linear response is appropriate. Linear relationships have been previously observed to describe the association between PM2.5 and mortality at PM2.5 concentrations below 35 ug/m3 (1-3). To make it more apparent to the reader where more of the PM values lie, we updated Figure 3 by making the 95% CI darker where 90% of the data lies. This would indicate to readers that above this PM level there could be less certainty.
We agree with the reviewer that understanding the potential non-linear effect is important. In response to the comment we have made this comparison available for reviewers through the addition of this comparison (df=5) as a supplemental figure and table for our admissions results (Figure S2, Table S2) and as a table for the readmission results (Table S3). Additionally, we indicate that including PM as a non-linear variable did not improve model fit in the Results section.
1. Li T, Guo Y, Liu Y, et al. Estimating mortality burden attributable to short-term PM(2.5) exposure: A national observational study in China. Environment international 2019;125:245-51. doi: 10.1016/j.envint.2019.01.073
2. Li T, Zhang Y, Wang J, et al. All-cause mortality risk associated with long-term exposure to ambient PM(2·5) in China: a cohort study. The Lancet Public health 2018;3(10):e470-e77. doi: 10.1016/s2468-2667(18)30144-0
3. Schwartz J, Laden F, Zanobetti A. The concentration-response relation between PM(2.5) and daily deaths. Environmental health perspectives 2002;110(10):1025-29. doi: 10.1289/ehp.021101025
3. The authors seem missed the following relevant paper:
https://gcc01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1016%2Fj.chemos
phere.2020.125913&data=02%7C01%7CRappold.Ana%40epa.gov%7C642e87a0d9c147341ac808d8
5bce5f08%7C88b378b367484867acf976aacbeca6a7%7C0%7C0%7C637360289194411679&sdata=
e1BwloRRHKUwiegY9zUfSya8L%2FQgitr%2FY1%2BLuy7InQg%3D&reserved=0

We thank the review for suggesting this recent article. Adding it as a reference in the introduction improved our rationale for assessing outcomes in patients living with CKD.
Reviewer: 2
Reviewer Name: Tazeen Jafar
Institution and Country: Duke-NUS Singapore Competing interests: I have no competing interests
Please leave your comments for the authors below The manuscript entitled “Association of short-term exposure to ambient PM2.5 with hospital admission and 30-day readmission in end-stage renal disease
patients: population based retrospective cohort study” is a well written manuscript. The topic is interesting, and statistical analyses are well done. However, I have some concerns:
1. My biggest concern is whether high PM2.5 is a proxy for the socially disadvantaged neighborhoods. The association between poorer zip codes with mortality and adverse outcomes is well
established in the US. I would encourage the investigators to account for neighborhood in the models to

determine the independent effect of PM2.5 on the primary outcome.
We thank the reviewer for allowing us to address this important consideration, that our results in part may be a result of underlying neighborhood socioeconomics. We addressed this concern by using a county-level socioeconomic variable from the US Census that would be comparable across counties nationally, the percent of individuals below poverty. Choosing the appropriate socioeconomic variable can be challenging in national studies, because many variables like median household income and educational attainment can reflect underlying regional differences.
In the admission models, modeling structure controls for county level SES as the conditional Poisson model was stratified on county. To control for county level SES across counties, we additionally stratified on the median (percent of individuals below poverty). The results from the high and low percent poverty models indicated no substantial departure from our original model. We show these results in Figure S2 and Table S2. Overall, we observed no significant difference by SES strata and have added this observation to the Results section.
In the readmission models, we added percent below poverty as an additional adjustment variable. The readmission risks now presented in the manuscript present results from the models with the additional adjustment. The magnitude of change by including the county-level socioeconomic variable was minor (< 1%).
We have updated our methods and results sections accordingly.
2. Additional model adjustments – models of admission adjusted for meteorological conditions, while models of readmission included additional patient-specific and hospitalization event-specific variables. Could the authors please explain why the patient-specific and hospitalization event-specific variables were not included in the model for admission? These variables could indicate the general characteristics
and overall health of the patient, which could be associated with admission?
Patient-specific variables were not utilized in the admissions models due to the hypothesized question. Our aim was to assess county level admissions; the quantity most commonly used to calculated excess burden due to air pollution. By aggregating to the county level, we were no longer able to report on the effects of individual characteristics. However, our county-month strata controls for a number of time invariant factors or factors that vary slowly over time (at frequency larger than monthly) such as pre-existing conditions, differences between counties, population size at risk etc. In response to the Reviewer's first request we have added stratification by SES.
In this analysis we also did not consider effect modification by pre-existing conditions because in this population chronic conditions rapidly evolve nor the time varying confounding where individual characteristics would include changes in individual's status due to PM exposure over time. That analysis is part of the future work and was beyond the scope here.
3. In addition, both models of admission and models of readmission did not not have direct proxies of patient health other than times of prior hospital admissions, such as years after dialysis, lipid levels, Creactive protein levels, etc. Are these variables available in the dataset? If not, this shall be mentioned in
the limitation sections as potential residual confounding factors.
Our hypothesis in the presented work was not focused on individual level sensitivities. Therefore, we did not use the data sources that are well suited for studying individual level sensitivities such as biomarkers of injury. Such data is however available from other sources such as Davita but is beyond the scope of this manuscript. We agree that this is a limitation and have added this to our limitations section (lines 399-400).
We were able to adjust the readmission models for an additional patient health factor, likelihood of death. The additional data of patient death date (additional censoring variable) allowed for the final model to express the cause-specific readmission risk (4). Adjusting for this patient factor changed our late-readmission estimates for all cause-readmissions to be higher and more similar to early-readmission estimates. Cause-specific estimates remained similar. We

have adjusted our methods and results sections and corresponding figures and tables to note these changes.

4. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601-9. doi: 10.1161/CIRCULATIONAHA.115.017719. PMID: 26858290; PMCID: PMC4741409.

4. Authors may consider adding a few lines in the discussion on what is the public health implication of
the current study.

Thank the reviewer for allowing us to further our discussion on potential public health implications from this study. We have expanded this discussion on lines 367-375.

VERSION 2 – REVIEW

REVIEWER	Shengzhi Sun Boston University School of Public Health USA
REVIEW RETURNED	15-Nov-2020

GENERAL COMMENTS	The authors have adequately addressed my comments. Thanks!

REVIEWER	Tazeen Jafar Duke-NUS Medical School Singapore
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	Revisions are satisfactory