Author’s response to reviews

Title: Ozone exposure is associated with acute changes in inflammation, fibrinolysis, and endothelial cell function in coronary artery disease patients

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We thank the reviewer for their comment. Here, we aim to more adequately explain our point of view, as well as provide the requested analyses.

The technique of future lagging (what we are calling the modeling strategy suggested by the reviewer) has fallen out of favor in air pollution epidemiology. Historically, the use of future lagging aimed to provide for observational experimental design, a kind of negative control, and nearly never (as in, we cannot find any such data-based/non-simulation papers) that carried out this technique with ozone. Currently, in epidemiology a version of this future-lagging technique is being considered for other much more complex purposes, but still has yet to be meaningfully
applied ozone whose temporal auto-correlativity is very well-known. Further, for these more complex purposes being currently considered in epidemiology, our dataset is of inadequate size to appropriately use this technique.

Since we are unable to determine from the reviewer’s comment exactly what the source of concern is, we make the assumption here that the motivation of the comment was to create a sort of negative control, wherein a biological outcome could not cause a change in future ozone.

In an experimental setting, a negative control is only appropriate when there is no relationship between the exposure of interest and the negative control exposure. Unfortunately, given the autocorrelative nature of ozone, future ozone is directly related to current ozone. In fact, ozone measure stop being strongly correlated with each other only when there is at least one, preferably two, months between the measures. Doing such an analysis would be out of the scope of the current manuscript, which was aimed at looking at acute responses due to ozone exposures.

Thus, completing an analysis looking at future lagging does not provide an adequate negative control for the relationship between ozone and our health outcomes. Since the desire for a negative control may not be the goal of the reviewer’s comment, we have carried out the requested analyses using ozone levels at a future lag of 5 days, despite the fact that it is correlated with lag0 ozone, and thus of unknown use as a negative control. In addition, we simulated ozone levels 10 times, that were based on nothing but a correlation with lag0 ozone of 0.5 to examine how often a statistical relationship would be found between simulated data and the outcome. For the future lag and the simulated lag, our results are summarized below:

Significant findings for lagging 5 days into the future, and the number of times the outcome were found to be statistically significant in simulated data.

**Single pollutant model**

- vWF (slope = -9.15; 95% CI = -17.4, -0.134, p value = 0.05, # findings in simulated model = 0)
- PAI.1 (slope = -26.2; 95% CI = 39, -10.8, p value = 0.002, # findings in simulated model = 1)
- QT (slope = 1.29; 95% CI = 0.175, 2.42, p value = 0.02, # findings in simulated model = 1)

**Two-pollutant model**

- PAI.1 (slope = -26.7; 95% CI = -39.4, -11.3, p value = 0.002, # findings in simulated model = 1)
- QT (slope = 1.28; 95% CI = 0.151, 2.42, p value = 0.03, # findings in simulated model = 1)

In the single pollutant model, only three outcomes were associated with the future lag model (PAI-1, vWF, and QT interval). Of those three outcomes, only one outcome was found to be associated with future and lagged ozone exposures (PAI-1); none of the other outcomes
highlighted in the manuscript that were associated with lag exposures to ozone were also associated with future ozone exposures. Therefore, we are confident that our analyses captured changes associated with ozone lagged exposures and are not anomalous findings. While we hope these analyses will assuage the reviewer’s concern we don’t believe it is appropriate to include them in the manuscript itself the for reasons listed above. We believe we will be criticized in the epidemiology community for inappropriately applying this type of approach to our small cohort. Of course, if he editor insists we include it, we will comply.