Reviewer’s report

Title: Exposure to Ambient Air Pollution and Calcification of the Mitral Annulus and Aortic Valve: The Multi-Ethnic Study of Atherosclerosis (MESA)

Version: 0 Date: 12 Sep 2017

Reviewer: M Barinas

Reviewer’s report:

The authors present interesting results from a longitudinal assessment of the association between ambient air pollution (specifically PM<sub>2.5</sub>, PM<sub>2.5</sub> weighted and NOx) and prevalence and progression of cardiac calcification (specifically mitral annulus and aortic valve calcification) in the well characterized MESA cohort. Although primarily null findings, these data are novel in that they look at progression of calcification in vascular beds previously not extensively studied in a large population-based cohort free of CVD. The associations of these vascular markers (MAC and AVC) with heart failure highlight the potential significance of these data. Major strengths of this study include the large sample size and population-based design, thus adding to the generalizability of findings, the comprehensive measurement and modeling of the exposures PM<sub>2.5</sub> and NOx and the availability of extensive data on potential confounders. The major limitation, as the authors indicate, is the short follow-up (only 2.5 years on average) and the age of the population that may limit their power to detect effects.

Significant emphasis is placed on the confirmatory CAC progression results throughout the manuscripts (abstract, results and discussion). This emphasis detracts somewhat from the conclusion of this paper. The rationale for including CAC progression during the same time frame as the AVC and MAC progression as a comparison appears reasonable but the emphasis on the these results is somewhat distracting.

Methods/Results:

It is not clear in the presentation of the progression analyses whether the authors used baseline, follow-up or cumulative exposure levels of air pollutants. Please clarify in tables/figures.

I recommend that some additional data with respect to the distribution of the outcomes be presented in order that the reader may be able to assess the appropriateness of the use of modified poisson regression. Are there too many zeroes to fit the Modified Poisson regression model with robust variance estimation?

Moreover, do the annual progression data meet a normal distribution that meet the assumptions of linear regression?

Did the authors consider whether there was a significant effect of PM<sub>2.5</sub> when NOx was also in the model without the interaction term?
Minor comments:

* Introduction, last paragraph - State the specific measures of ambient air pollution assessed.

* Methods, Figure 1 - It is a little confusing as to why the number of participants with missing F/U CT scans vary by cardiac calcification measure. Are not the same CT scans used for all 3 measures considered in this manuscript?

* Results - It may be helpful to reader to present percentages for AVC/MAC in Table 1. Can present it as part of header.

* It is interesting that there were more smokers in the group with AVC and MAC (Table 1). Is this surprising? There should be some mention of this in the first paragraph of the Results section where the population is described by AVC/MAC status.

* What is the overlap between AVC/MAC? Consider adding to text or Table 1 distribution of each in the other group.

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