Author's response to reviews

Title: Particulate matter components and subclinical atherosclerosis: common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study

Authors:

Sun Min (min0607_sun@hotmail.com)
Joel D Kaufman (joelk@u.washington.edu)
Kim Sun-Young (puha0@u.washington.edu)
Timothy Larson (tlarson@u.washington.edu)
Timothy Gould (tgould@u.washington.edu)
Joseph F Polak (jpolak@tuftsmedicalcenter.org)
Matthew J Budoff (mbudoff@labiomed.org)
Ana V Diez Roux (adiezrou@umich.edu)
Sverre Vedal (svedal@u.washington.edu)

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Author's response to reviews: see over
Title: Commonly-used approaches to estimating long-term exposure to fine particulate matter (PM2.5) components and subclinical atherosclerosis: a cross-sectional study in the Multi-Ethnic Study of Atherosclerosis

Review 1:
This manuscript reports the results from a cross-sectional analysis of the association between PM2.5 and several of its constituents with two markers of subclinical atherosclerosis, carotid intima-media thickness (CIMT) and coronary artery calcium (CAC). It also examines the relative impact of three different exposure metrics. The manuscript is an important contribution to the literature given: (1) the importance of studies linking PM2.5 to cardiovascular mortality (2) the increased interest in determining the relative toxicity of PM2.5 constituents and (3) the mixed results of previous studies of particulate matter and CIMT and CAC. The MESA cohort is well recognized for the quality of the data and the study team is experienced and known for its thoughtful analytical approaches.

Nevertheless, there are several issues that should be considered prior to acceptance. Major Compulsory Revisions
1. The exposure strategy was not entirely clear. In each of the MESA sites, the authors co-located one of their own monitors next the EPA chemical speciation monitor (CSN). Presumably this was to make full use of that data. However, in the Discussion, it is stated that only the MESA monitors were used in the study. It seems like more species, over a longer exposure period, could be used from the CSN. Was there any comparisons made between your monitor and the CSN species monitor? Also, you could assign 2000-2002 (or longer) readings from the CSN to a subset of study participants located close to the monitor. In addition, it is indicated that two-week samples of PM2.5 and its constituents were collected, but the equipment was deployed for over a year. It’s not clear if the monitors provided data for every two-week period for the 50-week average used in the study and weather there were extra requirements placed on data completeness for each two-week period.

RESPONSE: In each of the six city regions, one of the MESA Air monitors was collocated with an EPA CSN monitor. The CSN monitor measured concentrations over 24 hours on a generally one-in-three day schedule, while the MESA Air monitor measured concentrations over a two-week period every two weeks. Because the monitors were collocated, the CSN monitor provides no additional spatial information for either our nearest monitor or inverse distance weighted exposure measures. Also, we carried out analyses comparing 2-week averages of the CSN concentration measurements with the MESA Air 2-week measurements and found that the two networks did not provide compatible 2-week measurements, partly due to the different time periods of sample collection (24 hours vs. 2 weeks) and, for the carbon fractions (EC and OC), a change in the EPA laboratory measurement method. While it is true, as the reviewer notes, that the CSN monitor would have allowed us to make use of a
longer and earlier monitoring period, but at only one site, we elected to only use the MESA Air data that allowed us to take advantage of whatever spatial variability was present in concentrations within each city region. Yes, the 2-week MESA Air samples were obtained consecutively over the 50 weeks included in the analysis. This has now been made clear (see revised text below). There was very little missing data in the MESA Air monitoring data, so no completeness criteria were applied.

Revised text. Methods, p.9: “MESA Air and NPACT monitoring consisted of two-week samples of PM$_{2.5}$ obtained on Teflon and quartz filters for every two weeks during the study period (see below).”

2. A major concern is the cross-sectional nature of the study. As you indicate, the fact that the associations became null when MESA site was added to the regression model suggests that cross-site differences in CIMT is driving the results. Were there any repeated measures that could be matched with CSN readings so that the full benefit of the longitudinal cohort could be utilized? It seems that within-city differences could be investigated for the species, especially for Los Angeles, where there should be sufficient exposure contrasts. I am not clear about the statement in the Discussion “While we put most interpretive weight on models that did not control for metropolitan area, it may have been preferable to place more weight on findings from models with control for metropolitan area if the data had permitted it.” You did, in fact, control for metropolitan area. Maybe you should include regional and neighborhood variables from the Census to provide additional controls.

RESPONSE: We admit that the cross-sectional nature of the study is a limitation. We plan to carry out longitudinal analyses as the next phase of the analysis, but feel that initial reporting of cross-sectional findings is nevertheless valuable. As noted, we discussed the effect of site adjustment and interpretation of findings from site-adjusted models - top of p.24 (next to last paragraph of Discussion). While some effect estimates were essentially null after site adjustment, not all were; i.e., effect estimates for OC and silicon were very sensitive to site adjustment, PM$_{2.5}$ was somewhat sensitive, and sulfur and EC were not, although the width of the confidence intervals widened, as expected. As suggested by the reviewer, we did look at findings for just Los Angeles. The within-city analyses are hampered by the limited exposure variability, due partly to the use of nearest monitor and inverse-distance weighting estimates based on spatially sparse monitoring data. Even for Los Angeles, where one would expect larger spatial concentration gradients in some of the PM components, there was relatively little variability (Figure 2). Hence, findings for Los Angeles alone are not especially helpful, with a suggestion of associations for PM$_{2.5}$ and EC (neither statistically significant), but little evidence of associations for OC, silicon or sulfur. Use of the more sophisticated exposure estimation model predictions, as alluded to in the text, may allow more of the expected exposure gradients in Los Angeles to be captured.

Added/revised text: Results, p.15, last paragraph: “..., although the size of the
effect estimates for EC and sulfur remained essentially unchanged, and the effect of PM$_{2.5}$ was only moderately reduced.” Abstract, Results section: “In sensitivity analyses, effect estimates for OC and silicon were particularly sensitive to control for metropolitan area.”

Regarding a longitudinal analysis, while we had data on subsets of the MESA cohort from exams 2, 3 and 4, in addition to the baseline data from exam 1, this provided only an average of 2.5 years of longitudinal data. While we have performed preliminary longitudinal analyses using these data, and the findings will be included in the Health Effects Institute report of the NPACT study, because of the short follow-up period, especially for endpoints such as CIMT and CAC, we have little confidence in these findings and would prefer not to report them here. With the recent completion of exam 5, ten or more years of follow-up will be available for approximately half of the cohort. This will allow a more meaningful longitudinal analysis to be carried out.

We agree with the reviewer that the quote from the Discussion is not so clear. Revised text: Discussion, bottom p. 24: “While we put most interpretive weight on models that did not control for metropolitan area, it may have been preferable to place more weight on findings from models with control for metropolitan area if it had been possible to accomplish that without dramatically reducing variability in exposure.”

Regarding the suggestion to include neighborhood level variables in some of health models, we have carried out analyses in MESA that have included census tract neighborhood socio-economic variables for the purpose of assessing confounding and effect modification. In none of these analyses did the addition of neighborhood level main effects result in a meaningful change in estimates of air pollution exposure effect. We have made no revisions to the text in this regard.

3. Given some previous findings of associations between cardiovascular outcomes and silicon, the low concentrations found in these study sites should be mentioned in the discussion. Silicon was the only species which showed a decrease over time in several of the MESA areas. Also, correlation coefficients for Figure 3 should be provided.

RESPONSE: It is true that there is evidence for associations of short- and long-term exposure to silicon with cardiovascular outcomes in some studies. However, this is not a consistent finding. In the companion NPACT study in the forthcoming HEI report from our colleagues at New York University in which PM component effects for estimated in the nationwide American Cancer Society cohort, there was no evidence for associations of silicon with cardiovascular mortality. While it is true that the exposure variability for silicon may be limited, our findings regarding silicon are not unique.

Added text: Discussion, p.21. “While relatively limited exposure contrasts for silicon may have hampered our ability to detect associations with silicon, previously reported findings on silicon effects on cardiovascular outcomes have not been consistent.”
We agree that the addition of correlation coefficients would be helpful and so have now added them to the legend corresponding to Figure 3.

4. There should be some discussion of the biological plausibility (or lack of knowledge) for an association with CIMT but not CAC.

RESPONSE: We do not have an explanation for the lack of coherence in our findings for CIMT and CAC.

Added text: Discussion, 2nd paragraph, p.17. “While CIMT and CAC are highly correlated, they independently predict future cardiovascular events [17], suggesting that each provides somewhat different information on atherosclerosis and cardiovascular disease risk. CAC is a measure of plaque in the coronary arterial bed while CIMT can be regarded more as a continuous measure of generalized atherosclerosis. Our findings of associations with CIMT but not with CAC are consistent with earlier findings on PM in the MESA cohort [15] and may indicate differential pollutant effects on different vascular beds.”

Discretionary Revisions
1. Given that statins will alter CIMT and may impact CAC, it may be useful to stratify by statin use since it may mask the impact of PM2.5. It would be of interest to see the interactive effect of PM2.5 and species on non-statin users. In addition, some analysis of other potential effect modifiers would be of interest. Minor Essential Revisions In Table1, there is a double asterisk for Lipid lowering medication and it is not clear what that signifies.

RESPONSE: We agree. In addition to controlling for lipid-lowering medication use in our primary model (Model 2), we have now carried out an analysis restricted to never users of statins. Interestingly, the findings are nearly identical to those for the entire group of study subjects. We have not for this paper performed analysis of other potential effect modifiers, but agree this could be of interest. Table 1 was corrected.

Added text. Results, p.15: “In addition to controlling for lipid-lowering medications in our primary model, we carried out an analysis restricted to those who reported never having been on statin medications (n= 4,754); findings in this subgroup were essentially identical to those in the larger group (results not shown).”

EDITOR’S COMMENTS:
This is an important study given the interests on the possible effects of PM2.5 and its components on cardiovascular diseases. My concern is related to two aspects.
1. Confounders models. The justification for choosing model 2 and model 3 is not clear. Why this specific ranking of the confounders. In addition, smoking
status was used but not intensity and duration. Main reasons should be explained.

RESPONSE: We agree that the rationale behind the selection of health models could be made clearer. The choice of adjustment variables included in our primary model (Model 2) was based on the Framingham Risk Score, as noted in the text. However, Model 3 was not as clearly justified. Model 3 was intended to serve as a sensitivity analysis by adding control for variables from an extended set of potential risk factors that were not included in the Framingham Risk Score.

Text revisions. Methods, p.11. “An extended set of covariates was included in Model 3 that added potential risk factors not included in the Framingham Risk Score: level of education, ...” Discussion, first paragraph. “… to adjustment for additional potential risk factors and other PM$_{2.5}$ components.”

2. A clear justification of adjustment for metropolitan area should be given. It is unclear in the present form.

RESPONSE: We had attempted to justify including models that controlled for metropolitan area in the next to the last paragraph of the Discussion: “Although we included a reasonably comprehensive list of potential individual-level confounder variables in our health effect analyses, it is possible that uncontrolled confounding from unmeasured confounders associated with metropolitan area is present. This motivated control for metropolitan area in Model 4.” We have therefore not made a revision to the text in this regard, but if this is still felt to be insufficient, we can try to revise.

Additional revision: Figure 3 legend. “Correlation coefficients for 2002 and 2007 values: PM$_{2.5}$ (0.74), EC (0.91), OC (0.72), silicon (0.46), sulfur (0.79).”

We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

As stated above the formatting also requires some editing. We strongly suggest that you look at at least one or two published articles as well as reading the Instructions for authors as the title page is far from the requested format. Please remove the header throughout the manuscript. The title should be shortened and should include the study design, for example "A versus B in
the treatment of C: a randomized controlled trial X is a risk factor for Y: a case control study".

RESPONSE: We have changed the title to: “Particulate matter components and subclinical atherosclerosis: common approaches to estimating exposure in a Multi-Ethnic Study of Atherosclerosis cross-sectional study”. While still long, we are required by MESA to include the name of the cohort in cohort publications.

The semi-colons between the authors' names should be changed to commas. Remove the tables lines around the email address and insert the heading Email addresses with the addresses listed as author's initials: email address e.g. JS:joe.shmoe@university.edu. The address for correspondence etc. should be replaced by *Corresponding author and the * placed after his/her superscript number(s).

RESPONSES: We have include the emails in the title page as on other papers in Environ Health that we reviewed, but cannot find how we would add email addresses separately, with author initials preceding each email address as instructed.

Only the first letter of the headings should be capitalized. In the Abstract, remove the periods after the headings and move the text below the headings. After the Discussion section, insert the heading Conclusions stating clearly the main conclusions of the research and giving a clear explanation of their importance and relevance. After the Conclusions insert the headings List of abbreviations, Competing interests, Authors' contributions and Acknowledgements. The List of abbreviations should be formatted as abbreviation:term and separating the pairs with semi-colons in sentence format. In the References, remove the issue numbers. For the tables, all horizontal lines should be visible. Please also ensure that your revised manuscript conforms to the journal style (http://www.ehjournal.net/info/instructions/). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 29 April 2013. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

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