Author's response to reviews

Title: An indoor air filtration study in homes of elderly: cardiovascular and respiratory effects of exposure to particulate matter

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Response to reviewers.

We are most grateful to the reviewers for their constructive criticism which we have complied with and thus we hope improved our manuscript considerably. We particularly appreciate the suggestion to assess the effect in relation to the actual change in exposure levels in addition to the filtration as category, because of the rather large variation in the efficacy of filtration. As it turns out we do with that approach find a significant association between the actual reduction in the PM2.5 level in the bedroom and an increase in the MVF in particular after 2 days of filtration and in subjects not taking any drugs. We have added the data on this in a new figure, in Table 5 and in the text of the results section. It is, however, a post-hoc analysis and should be interpreted with some caution as explained in the discussion. The abstract also had to be shortened to include this result. Our responses are outlined below in red.

Reviewer number: 1

Minor Essential and Discretionary Revisions

1. The introduction highlights the dominant source of particles in the home come from indoor sources, yet the subjects for this study were recruited because they lived within close proximity to major roads. Perhaps the selection of subjects for future intervention studies should include persons known to have exposures to high concentrations of indoor air pollutants (environmental tobacco smoke, wood smoke etc) or should include measurements of indoor air pollution prior to enrollment.

R: We agree that efficacy of indoor air filtration is more likely to be demonstrated if there is a substantial exposure contrast and that will probably in our community require selection of subjects with high indoor levels based on screening of a large number of homes by actual measurements. This is supported by our new finding of an association between the actual PM2.5 reduction and an increase in MVF. We now present these data and have added a note to this specific issue to the discussion.

2. The manuscript would benefit from a clear hypothesis in the introduction.

R: We have specified our hypothesis in the introduction.

3. The studies were undertaken during a 7-month period - was this during the summer or winter months? It is plausible that the composition of PM will differ with season to explain the discrepancy between the findings reported in the present study and their previous studies (Am J Respir Crit Care Med. 2008;177(4):419-25).

R: The present study was performed during the winter season as our previous study was as now mentioned in the material and methods section.

4. Whilst this is the largest intervention study of air filtration performed to date it
would be helpful for the design of future studies to include details of how the sample size was derived. Was this based on power calculations and if so what change in microvascular and lung function was the study designed to detect?

R: The study was powered to detect an 8% change in microvascular function with type I and II error levels of 5% and 10%, respectively, as now stated in the statistics section.

5. Whilst I agree with the authors’ conclusions and suspect that the lack of effect from air filtration in this study is primarily due to the small contrast in exposure conditions between the intervention and sham periods, given their previous studies demonstrated improvements in microvascular function in subjects exposed to similar low concentrations of indoor particles it would be important to consider whether measurement error could explain their findings. When performed in the subjects’ home what is the reproducibility and repeatability of the primary pulmonary and cardiovascular end-points within and between visits?

R: We agree that the small and especially the variable exposure contrast as well as the more heterogeneous population may be responsible for the lack of effect of filtration as a category. This is supported by our new finding of an association between the actual PM2.5 reduction and an increase in MVF. We doubt that the lack of measurable effect could be due to measurement error. For the MVF and the lung function we had reasonably high repeatability between visits with a coefficient of variation of 18% and 20% on the crude data in this study not taking the air filtration or other time variables into account, respectively. Usually between-day coefficients of variation are 14-15% also with measurement in the subjects’ homes.

6. Further research in cities with higher ambient air pollution concentrations is warranted to address what is an important clinical and public health question. The manuscript would benefit from some discussion of ways that this question could be addressed in future studies.

R: We have included this relevant aspect in the discussion.

Reviewer number: 2

Major Compulsory Revisions

1) Please give the data on the time spent at home. Furthermore, indicate whether there is a difference between the time spent at home during the sham period and the filtration period. Test whether outcomes need to be adjusted for time spent at home in the filtration period.

R: We have included data on time spent at home during the two scenarios, which was similar, and tested whether adjustment for it had any bearing on the results.
Minor Essential Revisions

1) Please explain the rationale for including elderly with vasoactive drugs

R: The rationale was to study a more representative population of elderly with a possible higher susceptibility to effects of PM as now mentioned in the introduction. As it turned out these subjects might be less responsive to improvement of home indoor air quality.

2) Provide the rationale for the measurement of secondary endpoints in the background and refer to their hypothesized association with exposure to PM.

R: We have expanded the description of the biomarkers used and the rationale for their possible association with exposure to PM in the introduction with references.

Reviewer number: 3

Major Compulsory Revisions:

1. The composition/source of the particles is potentially very relevant to their health effects, and the authors acknowledge this when they state that “wood smoke is not likely to be particularly toxic…, whereas similar levels of diesel emissions have consistently shown impaired vasomotor responses.” Therefore, it’s important to provide more details on the exposure source(s) of this study population. Page 6 indicates that they were “in close proximity to major roads” but no additional details were given (the previous paper by Brauner notes that homes were <350 m from homes with >10000 vehicles/day). What were the mean/variation of road proximities in this study? Are there other important sources (e.g. point sources) in/near Copenhagen? Were these apartments or homes? In what months/seasons were data collected? How often were windows opened (which would affect HEPA filter effectiveness)?

R: We have included data on the distance to busy streets and specified that all homes were apartments in the Material and Methods section now. There are no relevant point sources of air pollution in the Copenhagen area. Data were collected over a 7 month period starting in November as explained in that section. Windows opening status, reported in diaries was in median 30 minutes/day, mainly away from the street side. This was similar for the periods with and without filtration as now reported.

2. I am concerned about the heterogeneity of the study population, which the authors acknowledge as a limitation (on page 15). The population was taking a range of drugs that would act on one or more of the study outcomes, and had morbidities that might also affect susceptibility to particles (2 with asthma, one with diabetes) but the study isn’t really large enough to stratify by these variables.
So, in effect, participants with a wide range of susceptibilities are being grouped together. The drugs are particularly problematic, as they might be markers of increased susceptibility, but the drugs might also act to attenuate the effect of particles (this is a well-recognized problem in the literature on air pollution and blood pressure). In short, I’m concerned that this is not a particularly useful population in which to conduct this study.

R: The choice of including subjects with morbidity and drug use was based on addressing a representative (although non-smoking) population of this age range. Whereas we did not have power to find small effects among the potentially susceptible or possibly less susceptible subjects taking drugs we did have power to exclude relevant effect among those not taking any drugs as now added to table 5 in analyses based on air filtration as a categorical variable. As it turned out the efficacy of the intervention was lower and not the least more variable for the exposure levels than expected and when assessing the effect per decrease in bedroom level PM2.5 we do find a significant improvement in MVF which as the reviewer suggests appears confined to those subjects not taking any drugs though interaction terms were not significant. Nevertheless, it is in accordance with findings of lower vasomotor responses in patients with cardiovascular disease exposed to e.g. diesel exhaust.

3. These were non-smoking individuals. Did they live in non-smoking households (i.e., did spouses, roommates, etc., smoke?)

R: The homes and households were strictly non-smoking as now better explained in the Material and Methods section.

4. The analysis methods are not adequately described. Table 4 suggests that each time point (day 2, day 7, day 14) was modeled separately in one analysis, and then grouped together in another analysis, but this was not explicitly described. Also, were participants with incomplete data included, or were the data matched (i.e., only participants with complete data during both intervention and control periods included)? If the latter, then why was it necessary to include adjustment variables that don’t vary temporally in a meaningful way over 4 weeks (BMI, age, gender)?

R: We have expanded the description of the statistical analyses with the different levels and explained that participants with incomplete data were included and that is why BMI, age and gender were adjusted for.

5. In this study the authors adjusted for baseline levels of the outcome measures, but they did not in their previous study (in which they saw significant effects on MVF). How sensitive were the results in this study to the adjustment for baseline levels?

R: In our previous study we had no measurements of the baseline levels of the outcomes and could not adjust for them. Analyses without baseline adjustment yield essentially the same results as with adjustment as now mentioned in the Results section.
6. There were mean reductions in air pollution levels with HEPA filtration? Were reductions noted in every home? If no, how many homes saw a decrease? What were the range of the increases/decreases in pollution levels with HEPA filtration (in other words, the mean reduction does not tell the whole story of what was happening in individual homes when the HEPA filters were turned on)

R: We have included the range of changes due to HEPA filtration in the individual homes and it was rather variable. As the reviewer suggests there was indeed an effect of this with a significant association between MVF and the actual change in PM2.5 in the bedroom and CD62L, although not for other outcomes.

7. The investigators measured a large number of exposures (PM2.5, ultrafine particle counts, black carbon, PAHs). But very little was done with these data. In addition to using a binary intervention/control variable in the models to evaluate the intervention, I suggest also modeling the effect of the continuous pollutant measurements.

- The authors seem quite certain that the reason for not seeing effects in this study (and seeing effects in their previous study) is the relatively small exposure gradient in this study. Why was the gradient smaller in this study, even though both studies were among “traffic pollution impacted” homes in Copenhagen? Is the difference due to fewer indoor sources in the present study? Or less impact from traffic in the present study. I would be amazed if changes in ambient PM2.5 levels in Copenhagen over time alone could explain a difference in baseline indoor levels from 13 ug/m3 to 8 ug/m3.

R: We think that it would complicate our present manuscript with multiple outcomes measured repeatedly during two scenarios to also include the modeling of outcome in relation to the measured levels of pollutants as such. We prefer to have them as descriptors of the effect of the intervention on the exposure here. However, we plan to include the measured indoor pollutant levels in a coming publication focused on concomitant outdoor measurements of pollutants by urban background monitoring and their associations with the outcomes which will be further expanded by additional biomarkers to be measured.

However, the reviewer’s suggestion led us to assess the effects on the biomarkers in relation to the change in the key exposure variable PM2.5 which was measured in both bedroom and living room throughout the study and which would allow us to adjust for the variable efficacy of the air filtration. As it turned out the MVF was actually significantly associated with the decrease in the PM2.5 reduction in the bedroom and not significantly with the living room reduction. Moreover, this effect was strongest after 48 hours and in subjects not taking any drugs, both in consistence with our earlier similar study with 48 hour intervention in a population not taking vasoactive drugs.

- We agree that reductions in outdoor pollutant levels in Copenhagen between the two study -period although significant are not the only explanation, but that less active indoor sources possibly due to more consciousness of potentially associated risks can have contributed to a smaller and more variable exposure contrast.

8. Related to the previous comment, there would seem to be many alternate
explanation for the different findings between the two studies, so I’m not sure why the authors place so much emphasis on the smaller exposure gradient in this study (I agree that it’s a possible explanation, but just one of several equally plausible explanations). For example, the studies differ in populations (apparently a less healthy population with more medication intake in the present study), adjustment for baseline measurements (adjusted in this study and not in the previous study), etc.

R: As we write the subjects were also to a lesser extent staying at home in the living room of the home were filtration was effective, mainly because this study lasted 28 days, whereas this was more feasible in our previous study with only 4 days in total duration. We agree that the more heterogeneous population could have contributed to a lack of a significant overall effect as suggested by the association between bedroom reduction in PM2.5 and MVF mainly in drug free subjects and after 48 hours of filtration similar to our previous study, whereas analyses without baseline adjustment yield essentially the same results as with adjustment.

Discretionary revisions:

1. I suggest also evaluating the amount of time spent indoors at home as a possible effect modifier.

R: We have included data on time spent at home during the two scenarios, which was similar, and tested whether adjustment for it had any bearing on the results.

2. I suggest adding a row to Table 1 indicating how many subjects took ANY medication (i.e. how many participants took a vasoactive drug OR a statin OR a cyclooxygenase inhibitor?).

R: We have included such a row in Table 1 and added analysis of effects stratified for the use of any drug in Table 5.