Author’s response to reviews

Title: Long-term exposure to air pollution and hospitalization for dementia

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Ref: ENHE-D-19-00108 “Long-term exposure to air pollution and hospitalization for dementia”

Dear Editor,

We thank you and the reviewers for the comments received. We think that the work considerably improved taking account of the raised points. We provided below a point-by-point answer.

Reviewer reports:

Editor's comments: We agree with the reviewers that the study has weaknesses that must be spelled out and discussed on more detail.
Reviewer #1: This article addresses an important question - the influence of long-term air pollution exposure and dementia. Unfortunately, the research conclusions are not clear due to the use of dementia hospitalization as the outcome ascertainment method. The authors should be commended for clearly stating the limitations of this outcome (which are substantial), but thorough analyses are also needed exploring these limitation before the article's main analysis results can be interpreted with any confidence.

We thank the reviewer for this comment.

Line 361. We changed the sentence “The main limitation of this analysis is the possible misclassification of cases” in “The main limitation of this analysis is the use of dementia hospitalizations as outcome, with a possible misclassification of cases” and we deepened the discussion in the lines below.

* The protective effect of air pollution for Alzheimer’s disease and senile dementia is likely driven by confounding factors. These same factors likely influence the vascular dementia results. Sensitivity analyses are needed to examine the robustness of these results. These could include a fixed effect for neighborhoods, more urbanicity measures (e.g. density, urban core, suburban place of residence), map of model residuals and Moran’s I, etc. If the authors can show what is driving these disparate results the main conclusions of the paper could be interpreted with confidence.

We concur with the reviewer that alternative analysis should be done. However, we were afraid that the use of neighborhood could mask the effect of air pollution, because air pollution variability is limited in a neighborhood (94 in the city of Rome) so that the contrast is not high enough. In addition, when we tried to include a fixed effect for neighborhoods, the model did not satisfy the hazard proportionality assumption. We then added a measure of population density in 1 km buffer from home, but it did not change the results.

The map of model residuals (see attached figure) did not provide clear hints.

* Unadjusted models should be shown in the supplement to inform residual confounding concerns.

We added an Additional file 3 with HRs

* A much more nuanced conclusion is needed given the major uncertainties with the outcome assessment. The use of hospitalizations to identify dementia cases (and all limitations) should be
introduced in the methods section and analyses conducted to explore the impact of these limitations on results.

We rephrased the conclusions:

“We found a positive association between residential exposure to NOx and ozone with first hospitalization for dementia in Rome. Exposures to particulate matter and nitrogen oxides were associated with hospitalizations for vascular dementia. We could not find a reasonable explanation for the negative associations we found in Alzheimer’s disease, and the results need to be interpreted cautiously, because on one side residual confounding of unmeasured lifestyle risk factors could play an important role, and on the other side using hospitalizations to identify dementia cases could lead to possible misclassification of cases.

Air pollution is pervasive, global, and harmful for health. Further efforts to reduce exposure in big cities are needed and have also the potential for beneficial effects on neurological health in elderly.

In method section we described our outcome as first hospitalization for dementia (and subtypes). We are aware that our outcome, so defined, does not allow to include all cases of dementia, and could lead to limitations in cases misclassification. For this reason we have argued this limit in discussion section of the article.

Reviewer #2: Thank you for the opportunity to review the manuscript, "Long-term exposure to air pollution and hospitalization for dementia ". This is a well written article assessing the relationship between annual average ambient air pollutant concentrations at residential address and the risk of hospitalizations for dementia. The authors address a critical issue for the scientific community as the evidence of brain impacts of air pollution is increasing.

We thank the reviewer for the comments and suggestions.

This manuscript should be accepted with minor revision based on my very few comments below:

1. Under Methods, the authors do not appear to have captured smoking history (including living with someone who smokes) of the study population, nor is smoking mentioned as possible confounder. Authors should address this in the discussion of study limitations.

We added in the text.

See line 181 in the methods and Line 373-377 in the discussion.
2. The novel aspect of this study is the evaluation of dementia subtypes. However the authors should state explicitly how they defined "dementia hospitalizations overall". I assume it is defined as hospitalizations for any of the dementia subtypes… but that is not clearly stated.

In lines 135 The first time we mentioned dementia overall we specified that we included all the codes previously declared.

3. The air pollution exposure assignment has serious limitations. One estimate representing the annual average for the year 2010 is assumed to represent air pollution exposures for study subjects followed from 2001 through 2013. The authors barely address this limitation. There is one sentence regarding one of the pollutants, NO2. Discussion of this limitation needs to be expanded. For example are there any long term air monitoring reports by the Italian government that show steady levels of all of target air pollutants in Rome? Have there been any major air pollutant regulations during the study period that may have impacted local air quality? How would the authors improve the exposure assignment if they could?

We better addressed this limitation. The assumption of the same spatial contrast over time is difficult to verify. In a previous study on NO2 land use regression models we were able to address the topic. However, we do not have sufficient data to do the same thing for other pollutants. The fixed monitors in Rome show a decline of air pollution in traffic sites (Cattani et al. 2010). Local air quality slightly improved in the traffic limited zone within the city center (6 km2) (Cesaroni et al. 2012), not enough to reach in 2010 concentrations for NO2 below the EU guidelines. We deepened the discussion on exposure assessment.

4. Related to the air pollution exposure measures are the assumptions about residential location. Authors didn't discuss the possibility of study subjects moving within Rome area during the study period. Was this information captured? If not or not utilized, how changing residential location within the study area could impact the exposure assignment should be addressed in the discussion.

We performed the analyses on subjects (88.4% of the study population) who did not move during the follow up (Supplementary files). The results are similar to those in the main analyses.

5. For Table 3, authors should include as a footnote the relevant national and/or EU air pollution standards for PM10, PM2.5, NO2, and O3.

We added the EU Air quality standards for annual averages including PM10, PM2.5 and NO2.
6. For table 4, it would help the reader if the authors also BOLDED or used an asterisk* to denote which results were statistically significant.

There is a tendency in the scientific journals not to pay attention to the results of the statistical testing but to the confidence intervals. For this reason, we did not bold statistically significant results.

7. The conclusion section is quite brief. The authors miss an opportunity to address the public health and policy implications of their findings. What's the big picture?

We rephrased the conclusions:

“We found a positive association between residential exposure to NOx and ozone with first hospitalization for dementia in Rome. Exposures to particulate matter and nitrogen oxides were associated with hospitalizations for vascular dementia. We could not find a reasonable explanation for the negative associations we found in Alzheimer’s disease, and the results need to be interpreted cautiously, because on one side residual confounding of unmeasured lifestyle risk factors could play an important role, and on the other side using hospitalizations to identify dementia cases could lead to possible misclassification of cases.

Air pollution is pervasive, global, and harmful for health. Further efforts to reduce exposure in big cities are needed and have also the potential for beneficial effects on neurological health in elderly.”