Author's response to reviews

Title: Association of traffic-related hazardous air pollutants and cervical dysplasia in an urban multiethnic population: a cross-sectional study

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Francesco Forastiere, MD, PhD
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Dear Dr. Forastiere,

My colleagues and I are pleased to submit our revised manuscript entitled “Association of traffic-related hazardous air pollutants and cervical dysplasia in an urban multiethnic population: a cross-sectional study” for consideration in *Environmental Health*.

We appreciate the time and effort taken by the reviewers to assist us in clarifying and strengthening the manuscript. We have addressed the reviewers’ comments and made the appropriate changes to the text of the paper. Additionally, we have provided a point-by-point response with our submission.

With best regards,

Philip Lupo, PhD
Authors’ responses to Reviewer 2

R2C1: the case definition: it is universally not accepted to put in the same group CIN1 and CIN2 and 3, because the link between CIN1 and cancer is not established at all while it is the link between CIN2/3 and cancer. In any case we could also accept a secondary analysis considering cases all CIN. It not acceptable in any case to include “HPV related modification” in the case definition for at least three reasons: a) this is not an internationally recognised histological class; b) by definition is related to HPV and I cannot understand how it could be analysed in a model in which HPV is a covariate (see below); c) such modifications are considered the expression of HPV reproductive phase in absence of any effect on cellular reduction, i.e. the way without any potential to transform the cell.

Response: We recognize the reviewer’s point related to CIN types, however previous peer-reviewed publications evaluating cervical dysplasia have analyzed all CIN types (1, 2, and 3) grouped as a whole. We have added references of recent studies that have used this case definition for cervical dysplasia in the Results section. In addition, we have reviewed our data and discovered that women coded with “HPV-associated changes” in fact also had a CIN 1 diagnosis in another biopsy taken at the same time. Therefore, these women were added the CIN 1 group and our current analysis only includes those diagnosed with CIN 1, 2, or 3; Table 1 as well as the Methods and Results sections have been modified accordingly.

R2C2: It is not acceptable to put a necessary cause as confounder in a model. The only reasonable way to analyse the data is stratifying by HPV status: in the stratum HPV+ it is possible to look for an effect of cancerogenicity. In fact, almost all the endpoints used in the case definition are histological consequences of the HPV infection and only rarely progress to cancer. It is not meaningful to make an aetiological explanatory model including HPV negative women and it is even worst to put the HPV status as covariate since it is the most extreme intermediate factor: a necessary cause. Analysing the association between outcome and HPV could be only useful to understand the accuracy of pathological diagnoses and laboratory methods. On the other hand, if the association is present also in the stratum of HPV negative women, this would be suggestive of an aspecific effect of benzene versus inflammatory effects that can simulate CIN.

The cervical cancer risk in the population should be divided in two kind of factors: those increasing the probability to be infected and those influencing the probability of having a neoplastic transformation given that a women is infected. The first should use HPV infection as end point (i.e. cases in this study design); the second should use cancer or CIN3 (CIN2/3 may be) as endpoint but only in the HPV+ population. To study the first kind of determinants I think the study population is too selected and HPV- women are not representative of the healthy population. With this population it is only possible to study the second kind of determinants.

Response: The outcome of interest in this manuscript is cervical dysplasia; not all dysplasias show evidence of HPV infection, especially mild dysplasias. We have provided references (please see the Statistical Analysis section of the Results) of other peer-reviewed publications evaluating cervical dysplasia that also included HPV-negative women in their assessment as well as adjusted for HPV infection status in their regression models.