Author's response to reviews

Title: Residential exposure to motor vehicle emissions and the risk of wheezing among 7-8 year-old schoolchildren: a city-wide cross-sectional study in Nicosia, Cyprus

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Author's response to reviews: see over
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The Editor, Environmental Health

Dear Editor,

Re: Residential exposure to motor vehicle emissions and the risk of wheezing among 7-8 year-old schoolchildren: A city-wide cross-sectional study in Nicosia, Cyprus

We are pleased to accept your offer to resubmit a revised version of the above article. Please note that we have made all the changes suggested by the editorial team. For example, the title of the manuscript has now been changed to “Residential exposure to motor vehicle emissions and the risk of wheezing among 7-8 year-old schoolchildren: A city-wide cross-sectional study in Nicosia, Cyprus” to more clearly indicate the design of the study. Furthermore, we have removed the keywords and word count from the title page and formatted the e-mail addresses based on your instructions. We have also corrected the referencing, removed the italics from the text and made horizontal lines in the tables visible.

More importantly, we would like to thank the reviewers for their constructive comments and suggestions. We have now addressed all the issues and recommendations raised by the reviewers. Below, please find our point-by-point responses in the order that were raised as well as relevant action. Corresponding changes are also highlighted in the manuscript. As a result, we also had to make some additional minor editing changes.

We look forward to receiving your response.

Yours sincerely,

Nicos Middleton, PhD
Assistant Professor in Research Methodology and Biostatistics
Reviewer 1: Francesco Forastiere

Major revision –
We agree with both the reviewers that we may have over-interpreted the observed non-linearity in the relationship between symptoms and traffic emissions. The relatively small size of the study and the nature of the exposure assessment do not permit inferences about the shape of the exposure response function. We have now removed any mention of a possible threshold effect from the abstract and revised the conclusion in the manuscript. Furthermore, we now mention that the observed non-linearity may be a product of the small size of the study, exposure misclassification or even the nature of the single symptom outcome investigated here. For example, unlike current wheezing, history of wheezing generally displayed a more stepwise relationship with exposure – see Discussion, Traffic emissions and the risk of wheezing.

Minor revisions –
1st para – We have now clarified in the abstract that the exposure indicators used here refer to emissions and not concentrations.

2nd para – We certainly agree with the reviewer that the literature is much wider. It was neither our intention to suggest that we have covered the vast array of relevant studies in our reference list nor such a review was the aim of this article. We had now referred to matter in the Background section of the paper in this manner “…While it is not the intention of this study to systematically review the large body of evidence, it is reasonable to say that the majority tend to report positive effects…” and so on. Furthermore, we followed the reviewer’s suggestion to expand slightly on our discussion about the validity of self-reported exposure measures – see first paragraph in the Discussion, Exposure Assessment.

3rd para – Table 2, which previously presented associations between reported symptoms and the range of participants characteristics, has been removed as we agree with the second reviewer that it may distracts from the main message (see below). A brief discussion on the key messages remains in the text. Crude numbers and prevalence, previously only mentioned in the main body, have been now been added to Table 3 (which as a result of removing the previous table is now appearing as Table 2).

4th para – Rather than graphically, effect estimates with regards to the cumulative measure of exposure are now presented in tabular form (see newly added Table 3). In other words, Figures 3 and 4 have been removed. As a result, we have decided to add two new figures which present some of the results of the sensitivity analyses (i.e. restricting to those addresses geocoded at the house levels or considering exposure at the school location), previously only covered in the text.
Reviewer 2: Bert Brunekreef

1. Most evidence on the association between exposure to traffic emissions and experience of asthma symptoms in children comes from large cities in Europe and North America. Similar evidence in the context of smaller cities or other parts of the world has been limited. It was certainly nice to see that the first reviewer also highlighted this in his report.

This study was based on a city-wide survey with high participation of all 7-8 year-old residents in Nicosia, a relatively small Mediterranean city where both geoclimatic conditions and outdoor activity patterns may differ considerably from other much larger European capitals. Of course, we should point out that the aim here was not only to investigate (confirm or refute) any association between asthma symptoms and residential exposure to traffic emissions. To a large extent, we were empirically driven to explore whether the observed pattern of effect might explain the higher prevalence of asthma recorded in Nicosia compared to the rest of the island. Needless to say that for Cypriot public health research and policy, this study has tremendous implications since (as we explained in Methods, Data and Data Sources) we are not aware of any other Cypriot epidemiological study that has employed GIS. We have explained this in the last paragraph of the Background section of the revised manuscript.

2. The digital map was completed in the year 2006. The work involved georeferencing and informing a series of raster maps originally provided by the Cyprus Cartography Services (dated 2002-2005, at a scale ranging from 1:2500 to 1:7500) with the use of 20 ground-teams. The resulting maps have scale 1:5000 and a precision of <3m. This was the first and only digital vector maps of Cypriot cities available at the time of this research. While the maps are more recent than the data collection (and may thus include roads that appeared or reclassified into main roads since), only the subset of roads included in the 2001 Emissions Inventory were considered in the analyses, which represents more closely the street network at the point in time that the questionnaire was administered. We have added this information in the Methods, Data and Data Sources section of the article.

3. The 2001 Emissions Inventory, performed by the Air Quality Section of the Ministry of Labour in collaboration with the University of Stuttgart, was the first (and currently only) systematic effort in estimating emissions from various sources on the island, including the road sector. The Ministry’s report describes a number of limitations regarding the application of the COPERT methodology mainly due to the lack of a comprehensive database of the car fleet on the island. Thus, certain modifications and assumptions had to be made including the assumption of uniformity in the composition of the car fleet geographically. Due to lack of other routine sources of traffic related data in Cypriot cities, and despite their limitations, this was the only source of relevant data other than proximity measures – we have now provided further details in the third paragraph of Methods, Data and Data Sources. We also specified the unit of measurement as kg/km per day and in Methods, Outcome and exposure assessment, we explained
that rather than restricting the calculation to the nearest or the road with the highest levels, the cumulative measure considers any road that crosses the specified buffer. This crude measure does not represent total mass within the buffer, thus why it was only used as categorical rather than continuous variable. Finally, we explained in the Strengths-Limitations section of the revised manuscript that despite the crude nature of exposure assessment, the consistency in the direction and pattern of effect estimates across the different definitions of exposure (i.e. proximity or emissions based) is reassuring.

4. In addition to parental history of atopy, we also adjusted for personal history of hay fever and eczema as allergic sensitization (also found to be more pronounced in Nicosia than elsewhere) may act as a confounder in the association of interest. As the reviewer indicates, several studies have shown associations between traffic exposure and allergic sensitization, even though the evidence is less consistent. The Vesta case-control study in France has shown that early-life exposure to traffic pollution is associated with asthmatic symptoms even after adjusting for both personal and parental allergy. While we agree with the reviewer about the danger of over-adjusting when considering co-morbidity (for example, if the direction of association between allergy and asthma is assumed to be causal), this has not been the case here since, other than the expectedly larger standard errors, the magnitude of effect remained largely unaffected suggesting that the association between traffic pollution and wheeze was independent of allergy. Excluding hay fever and eczema from the models does not alter our conclusions and is evident from the fact that effect estimates have not attenuated during the separate stages of adjustments. Furthermore, it has been suggested that the association between traffic pollution and asthma may be more pronounced among atopic subjects. Of course, our study was under-powered to address this issue; nevertheless there was generally no statistical evidence for such an effect modification. We have now provided a discussion of these issues in the Methods or Results accordingly.

5. Table 2 has now been removed from the manuscript. The main inferences about the association between asthmatic symptoms and participant characteristics or co-morbidity are only briefly presented in the main body of the text – see para 5 in Results.

6. In the absence of time-activity data for these children, we considered a weighted exposure at home and at the school location as a sensitivity analysis. Due to the large number of Tables and Figures, we had previously chosen to mention the results of this analysis only in the text. Since we have now replaced Figures 3 and 4 with a table, we are now presenting these results along with the results of the other two sensitivity analyses performed where (a) peripheral areas (where the coverage of the emissions inventory was poorer) were excluded and (b) only addresses geo-coded at the house level were included see newly added Figures 3 and 4. Only effect estimates for current wheezing are presented; however, inferences for the other two outcomes were similar.
7. While the observed pattern of effect persists even after excluding peripheral areas or inaccurately geo-coded addresses, we agree with the reviewer that the nature of the study does not allow us to draw firm conclusions about the shape of the exposure response function. As we have already mentioned above (see response to reviewer 1), we have now removed any mention of a threshold effect and recognized that the observed pattern may be a product of the small size of the study or exposure misclassification – see Discussion, Traffic emissions and the risk of wheezing.

8. Any reference to the association between air pollution and respiratory outcomes from studies with a time-series design has been removed – previously at the end of the first paragraph in the Discussion, Traffic emissions and the risk of wheezing.