Author's response to reviews

Title: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health

Authors:

Daniela Nuvolone (daniela.nuvolone@asf.toscana.it)
Roberto della Maggiore (roberto.dellamaggiore@isti.cnr.it)
Sara Maio (saramaio@ifc.cnr.it)
Roberto Fresco (roberto.fresco@isti.cnr.it)
Sandra Baldacci (baldas@ifc.cnr.it)
Laura Carrozzi (carrozzil@ifc.cnr.it)
Francesco Pistelli (pistellif@ifc.cnr.it)
Giovanni Viegi (viegig@ibim.cnr.it)

Version: 2 Date: 29 November 2010

Author's response to reviews: see over
Authors: We thank the reviewers for their constructive comments. We have modified/rewritten our manuscript following their suggestions. We hope to have adequately addressed their comments.

Reviewer’s report

Title: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health

Version: 1 Date: 6 September 2010
Reviewer: Emilie Stroh

Reviewer’s report:

This study is, although an old study design, due to the high quality of data of importance within its field.

Major Compulsory Revision

In this study most of the results are presented using three different p-values: p<0.1, p<0.05 and p<0.01. In some sections results with p-values of <0.1 and <0.05 are described as “borderline significant”, however in most part of the document this is not the case and for results with a p-value of <0.1 this is often described in the text as “significant”. If this is the authors view it would be interesting to have a section describing why p<0.1 is considered as being significant especially with non-convincing confidence intervals (where presented)? I do not find these results convincing and there is no section in the discussion where these results are critically reviewed by the authors themselves.

We thank the reviewer for this comment. A p-value less than 0.05 was considered statistically significant. We have modified/rewritten the manuscript (Results section and notes in tables 2-6) to better describe the statistical significance of results.

Discussion section was completely reorganized, adding a more critical review of results.

In the abstract they state that: “Results were confirmed in long-term residents who showed even higher risk”. According to the last section on page 12 half of the OR:s presented are lower for the long-term residents – this is not critically considered in the discussion either.

After this criticism, we decided to not include the analyses carried out on the long-term residents subsample due to the fact that residents for more than 5 years (long term residents) represent about 90% of our sample, thus stratified analyses probably do not provide added valuable information. Instead, in order to consider possible multivariate relations, time of residence has been directly included in logistic analyses.

The discussion consists mainly of a summary of similar work (that could have been fitted into the background section instead) and results that confirm their own. I lack a more critical review of this study’s results. As it is only the study’s advantages are mentioned and none of its disadvantages. There is a lack of discussion regarding the uncertainties that some of the results are showing as well as potential confounders and the study design.

We realize not having been detailed in the original manuscript on these issues. Following all reviewers’ suggestions, the discussion section has been completely reorganize through updating
I also lack information and a critical discussion about the individual occupational exposure. How was this exposure classified? How was this variable defined and on what grounds? Since twice as many men are occupationally exposed (to what??) compared to the women – this might cause the differences in exposure seen in table 2-4? Why are these analyses not adjusted for “occupational exposure” as well?

Following reviewers’ suggestions, in a new paragraph completely dedicated to potential confounders we have better described the occupational exposure of the sample. In order to take into account the different distributions of occupational exposure by gender, occupational exposure was considered in multiple logistic regression models. With regard to continuous variables, as asked from other reviewers, we have also fitted multiple linear regression models adjusting for occupational exposure too: same associations as in table 4 were found. Thus, we decided not to add these data in the text.

Minor Essential Revision

Abstract (p2):
Here you state that you use GIS to examine whether distance from main roads has effects on respiratory health status. However; what you do examine is the effect from one major highway.

Thank you for your suggestion; we have modified the abstract to better describe the aim of the study, i.e. to examine the adverse effects of living near a major road.

The analyses were not restricted to long-term residents but analysed as a sub sample.

As previously described, we decided to eliminate this section on long-term residence.

Methods/Background (p5):
In this section (first sentence) you state that the surveys were carried out “before” (85-88 and 91-93) when it should be “during”?
One page out of 1½ is devoted to describing the previous survey (conducted during 1985-1988) and its different zone’s and measures. This information is more misleading than guiding since this precious study has nothing to do with the present one nor the aim of the study and the results are not compared to it either.
It would be much more helpful if the “new” survey (conducted in 91-93) where described in more detail (i.e. the area, the number of habitants, the Tosco-Romagnola highway and number of vehicles/day etc).

Following all reviewers’ suggestions, we decided to eliminate comments on the first survey and to focus on the second survey (1991-93). We have rewritten this section adding more information on study area, Tosco Romagnola road, and study design.

Methods/Exposure assessment (p6):
Figure 3: This map is really illustrative but the legend needs to be remade.
Objects that are presented in a map must be described in the legend, in this
case: the highway, major streets, buildings and the different zones. Also the heading is misleading; those dots are not ONLY showing the “samples home residences” but rather “their proximity to the Tosco-Romagnola highway”.

Following reviewer’s suggestion, Figure 3 has been modified

Methods/health outcomes assessment (p7):
Did you check if there were any geographical or socio-economic clustering in the number of study subjects that choose to participate in the clinical tests?

We thank the reviewer for this comment. Chi-square test results for confounding factors between subject participating and not participating in lung function and allergological test are reported in the following table.

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<th>Lung function test</th>
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Respect to those not participating to lung function and allergological test, subjects involved were more likely men, smokers, young/adults, exposed to passive smoking and with high education levels.

The text has been modified.

I lack a section under “Methods” about socio-demographic information/potential confounders. What information was obtained from the survey? Why did you choose to incorporate some information in this study and not other (for example: why were “indoor exposure left out?).

Following reviewer’s suggestion, we added a new paragraph completely dedicated to potential confounders and the great amount of data collected through questionnaire. We had previously addressed the indoor air pollution topic, published in other papers (Simoni M, Jaakkola MS, Carrozza L, Baldacci S, Di Pede F, Viegi G: Indoor air pollution and respiratory health in the elderly. Eur Respir J 2003, 40:15-20. Simoni M, Scognamiglio A, Carrozza L, Baldacci S, Angino A, Pistelli F, Di Pede F, Viegi, G: Indoor exposures and acute respiratory effects in two general population samples from a rural and an urban area in Italy. J Expo Anal Environ Epidemiol 2004, 14:144-152); however, daily activity pattern, and in particular hours spent at home, was considered in the analyses (tables 2 and 6).

The middle section at page 9 would fit better in such a section than squeezed in under statistics. It would also be interesting to know if you had information about employment/unemployment since duration at the home address during the day would increase the exposure from the highway and (for example) if your study subject consisted of a large proportion of “housewives” these might be more exposed from the source in question and might explain some of the differences that can be seen in the gender stratified results.

As above described, all these information have been added in a new paragraph completely dedicated to potential confounders and they were used in analyses. Information about hours spent at home during the day have been included in the analyses through the use of daily activity pattern data.

I lack a section where you describe why choose to classify your study subjects in those age groups. Why cut off at 25 and 64?

We chose the same age groups used in our previous article regarding the respiratory health of the same sample of Pisa (Viegi G, Pedreschi M, Baldacci S, Chiaffè L, Pistelli F, Modena P, Vellutini M, Di Pede F, Carrozza L: Prevalence rates of respiratory symptoms and diseases in
general population samples of North and Central Italy. Int J Tuberc Lung Dis 1999, 3:1034–1042); this choice will permit the comparison with our previous results. Moreover, these cut-off permit to identify possible effects on more susceptible categories (younger and elderly). At last, subjects below 25 years of age are mostly unemployed, have worked for few years, this they are a population group interesting to study in this context because they likely have less potential confounding from occupational exposure.

Statistical analysis (p7-9):
You state that you had information about: “education” and “subjective perception of environmental pollution at own home” however these variables have not been used in this study.

As above described, all these information have been added in a new paragraph completely dedicated to potential confounders, they were used in analyses.

Why did you not adjust for occupational exposure in all your analysis?

As previously described, occupational exposure was considered in multiple logistic regression models. As regards to continuous variables, as asked by other reviewers, we have also fitted multiple regression models adjusting for occupational exposure too: similar associations were found. Thus, we decided not to add these data in the text.

Results (p10-12):
Table 1: Here you have added “Education” – however you do not use this variable in your analyses.

We apologize for this mistake: although not written in the original manuscript, education had been considered in logistic regression, as it is now specified.

Where there any differences in “Time of residence” in the different exposure groups? People living close to a major highway might be more prone to move for example.

As reported in new table 2, no significant difference in the time of residence was observed between subjects living at different distances from main road.

Is it really possible that there are people living less than 2 metres from a major highway?

As noticed by all reviewers, the term “highway” was misleading. Indeed in Italy the term is ‘strada statale’, i.e. a major road under the responsibility of the state government, as opposed to less important roads under the responsibility of Provincial or Communal government. We removed the term highway from the text; the correct term is “main road”, thus it is possible that homes are right next to the road which, as was usual in the past, passes through inhabited zones of different localities. Characteristics of Tosco Romagnola have been better described in method section.

Table 3: You have not defined the term “DLCO”.

Thank you for this suggestion. The term DLCO has been defined in the text.
Table 4/p11: The “observed trend” for skin prick test and bronchial reactivity in male is not significant and very weak.

Following reviewer’s suggestion, we have modified the text and underlined this comment.

Table 6: this table is redundant – the information is already obtained in table 3 and 4. However the numbers (n) between table 3 and table 6 does not correspond.

Thank you for this suggestion. Table 6 has been eliminated. For the sake of clarity, it is to mention that the lower numbers in table 3, with respect to those reported in table 6, were due to missing values in adjusted analysis of variance.

Discussion:
Needs to be rewritten (see major compulsory revisions)

As previously described the discussion section has been completely reorganized through updating references, adding more comments on study advantages/disadvantages, study design and potential confounders.

Conclusion:
Could be expanded
Thank you for this suggestion. The conclusion has been expanded.

Discretionary Revision
It is interesting to notice that AFTER the construction of the highway the levels of TSP and SO2 decreases in the area - why is that? Maybe this should be addressed in this section (Method/background) since this comparison is being made?

Following all reviewers’ suggestion, section on description of the first survey was completely eliminated from the text. Major details on the comparison between the two survey are reported in Viegi et al. 1999 (Viegi G, Pedreschi M, Baldacci S, Chiaffi L, Pistelli F, Modena P, Vellutini M, Di Ped F, Carrozzi L: Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. Int J Tuberc Lung Dis 1999, 3:1034–1042; Baldacci S, Carrozzi L, Viegi G, Giuntini C. Assessment of Respiratory Effect of Air Pollution: Study design on general population samples. JEPTO 1997;16:77-83). Anyway, the levels of conventional pollutants were reduced probably because the heavy traffic (mainly trucks) was diverted from the zone of residence, since the newly constructed highway is far from the investigated zone.

Figure 1: The map would be much more appealing if you removed those buildings that are not within “Pisa” or “Cascina” municipality (in my opinion the buildings could be removed altogether from this map to add clarity). The scale bar should be presented in km for such large areas.

Figure 1 has been remade, using colours. We decided to leave buildings in the map in order to better depict study area characteristics. Scale bar has been corrected.

Figure 2: This is a good map but I think it could be even clearer if the buildings were removed. The scale bar should be presented in km for such large areas.
Figure 2 has been remade, using colours. We decided to leave buildings in the map in order to better depict study area characteristics. Scale bar has been corrected.

Methods/health outcomes assessment (p7):
It would add clarity to your paper if you added the abbreviations used in the tables to this section.

Thank you for your suggestion: the abbreviations used in the tables have been added in the text.

Although the information in table six is redundant (already added in table 3 and 4) it would be better to refer to it in this section than later on.

As previously described, table 6 has been eliminated.

The choice of “exposure groups” could be more clearly defined (p6). As presented in the discussion many similar studies have used a cut off at 50m from major roads for the highly exposed group. Also the choice of reference group could be debated depending on the size and intensity on the highway (number of vehicles/day etc.) a reference group consisting of individuals living as close as 250m from the highway could be discussed.

Study area characteristics and Tosco Romagnola road features have been better described in methods section and some considerations on the choice of exposure groups were added.

Statistical analysis (p7-9):
This section would gain a lot if you tried to organise it a little bit. My suggestion is that the first section (with the definition of the different health outcomes) should be fitted into a list, such as:
1) Chronic cough (or plegm)
   Producing cough (or plegm) apart from common …
2) Attacks of shortness of breath with wheeze
   Any attack of shortness of breath ….

Following reviewer’s suggestion, this section has been modified for the sake of clarity

Also; the section about confounders could be moved to “methods” (see earlier suggestion).

As previously described this section has been completely reorganized.

Results (p10-12):
It would suffice if you presented the average distance to the subjects home without any decimals.

Thank you for this suggestion, distance has been now presented without any decimals

It would be easier to read the results from the “long-term” residents if you put these: in table 5, in a table of its own or as a list.

As previously described, results on long-term residents have been no more included.

Be consistent: sometimes you use the term “main road” and sometimes
As noticed by all reviewers, the term “highway” was misleading. We removed this term from the text; the correct term is “main road”. Characteristics of Tosco Romagnola road have been better described in method section. In the past, Tosco-Romagnola road was the main street connecting Pisa to Florence, crossing the urban centres. Then, at the beginning of 90s’ a new road connecting Pisa to Florence (similar to the American highway) was opened, far from the investigated zone; this new ‘highway’ has reduced the number of vehicles crossing the Tosco Romagnola road, in particular the heavy traffic like the trucks.

Why do you make comparisons or refer to US questionnaires or systems? Their questionnaires or address system is not international standard.

We thank for this suggestion: this topic has been eliminated from the text.

Do you by civic number mean “house number”? Maybe you should consider using another term in that case since it might be confused with “identification code/number”.

We thank for this suggestion: the correct term is “house numbers”, we modified the text.

(2) However, since the construction of the highway offers a natural experiment of changing exposure levels, the authors may want to consider looking at incidence of symptoms in residents of the areas where the highway was built, especially if individuals participated in both surveys. This may be outside the scope of this paper, but would be interesting.

Thank you for this suggestion; we will perform longitudinal analyses to be reported in a subsequent paper.

(2) In the Background, the authors mention levels of TSP and SO2 in the study area. Have they chosen not to use these pollutant measures directly because of sparse monitoring density?

As rightly noticed by the reviewer, pollutants measures were very sparse, so that we decided not to use in this study, but just to refer to the mean values as provided by the Pisa Province Unit of the Environmental Protection Agency.

(3) Figure 1 (and the rest of the Figures) would be much more effective in color.

Figures have been remade, using colours.

(4) In the first paragraph of the Exposure Assessment section (and thereafter) the authors refer to distance to the "main road". Does this refer to the Tosco-Romagnola highway? This should be explicitly stated, since the Figures include numerous additional roads, and the Background also refers to a large highway connecting Pisa and Rome.

We apologize for having not gone into detail in the original manuscript on these issues. Following all reviewers’ suggestion, we have modified the text to better describe the study area: only one road (Tosco Romagnola) was considered in the study. The term “highway” was misleading. Authors removed this term from the text; the correct term is “main road”. Characteristics of Tosco Romagnola road have been better described in method section.

(5) In the first paragraph of the Statistical analysis section: “or stopping while walking in plain to take breath (III grade dyspnoea)” is unclear.

We thank for this suggestion, the correct form is “stopping while walking on ground level to take breath (III grade dyspnoea)”, also reported in the text.

(6) The authors should note if there were any major differences (in age, other potential confounders, traffic exposures, etc.) between individuals providing information on skin prick tests, IgE, lung function tests, etc.

We thank the reviewer for this comment. Chi-square test results for confounding factors between subject participating and not participating in lung function and allergological test are reported in the following table.
### Lung function test

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### IgE test

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### Prick test

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<th>yes</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>37.7</td>
<td>57.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>smokers</td>
<td>19.7</td>
<td>26.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ex-smokers</td>
<td>26.6</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>high education</td>
<td>15.8</td>
<td>33.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>medium education</td>
<td>17.7</td>
<td>34.9</td>
<td></td>
</tr>
<tr>
<td>8-24 age group</td>
<td>11.4</td>
<td>27.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-64 age group</td>
<td>50.9</td>
<td>69.3</td>
<td></td>
</tr>
<tr>
<td>passive smoking exposed</td>
<td>47.2</td>
<td>60.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>occupational exposed</td>
<td>42.8</td>
<td>41.2</td>
<td>0.469</td>
</tr>
</tbody>
</table>

Respect to those not participating to lung function and allergological test, subjects involved were more likely men, smokers, young/adults, exposed to passive smoking and with high education levels

The text has been modified.
(7) The authors should note how the % predicted spirometry values were determined.

We thank for this suggestion. A reference had been added on this topic.

(8) In the background, there is some mention of available time-activity information. Was this not considered as a confounder or effect modifier?

Following reviewer’s suggestion, we added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including time-activity (hours spent at home) data. Time-activity has been now used in the analyses.

(9) The sentence "Residences within 100m were 585 (28.4%; mean distance 38.8m; median distance 32.9m); between 100m and 250m were 611 (29.6%; mean distance 167.2m; median distance 169.8m); between 250m and 800m were 866 (42.0%; mean distance 424.5; median distance 398.1m)." is awkward.

We thank for this suggestion, this section has been modified.

(10) In the results, the authors note a large number of different tests for significance (Tukey, Least Significant Difference (LSD) for lung function; Analysis of variance, Tukey, Bonferroni, LSD, and Duncan for bronchial activity). The use of these multiple tests should be explained in the Statistical Analysis section. Ideally the authors would focus on one measure per association.

We agree with reviewer’s suggestion. Analyses of variance were performed to compare means among the distance classes. The other test (Tukey, Duncan, LSD, Bonferroni) are post hoc range tests and pairwise multiple comparisons to determine which means differ. As these tests have yielded same results, for the sake of clarity we have decided to report only Tukey test results.

(11) The paragraph highlighting the results of Table 5 would be much easier to follow if all of the ORs and 95%CIs (which are already presented in the table) were not repeated.

We thank for this comment: 95% CI and OR were eliminated from the text.

The authors should also note that many of their outcomes were not significant, and in some cases were negatively associated, in the intermediate exposure group.

We agree with the reviewers and some considerations on this topic were added in the discussion section.

(12) Table 6 presents the sample sizes by gender and exposure group. This may be more useful before the results tables, though it does seem to have been incorporated into Tables 3 and 4. It may just be worth reformatting Table 5 to also include this information.
As raised by other reviewers too, table 6 has been eliminated. Relevant information are provided in table 4.

(13) Overall, the discussion would be stronger if more work was put into summarizing groups of studies. This may be somewhat difficult due to the different "exposed" cut-offs used in each study, but if possible at all would be helpful. It may be easier to put together a table comparing the key findings of this paper to others.

Following all reviewers’ suggestion, discussion section has been completely reorganized. We think it may be sufficient, also because we had the impression that all the reviewers suggested to reduce the amount of illustrations. However, we have prepared the table and we will add it in the manuscript if the editors will permit to do it.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population sample investigated</th>
<th>Health outcome</th>
<th>Exposure</th>
<th>Measures (95% CI*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindgren A, 2009</td>
<td>9319 subjects (18-77 yrs) Sweden</td>
<td>Asthma diagnosis Asthma symptoms COPD diagnosis Chronic bronchitis symptoms</td>
<td>Living within 100m of a major road</td>
<td>OR: 1.40 (1.04-1.89) 1.29 (1.00-1.67) 1.64 (1.11-2.41) 1.53 (1.10-2.13)</td>
</tr>
<tr>
<td>Garshick E, 2003</td>
<td>2628 male adults USA</td>
<td>Persistent wheeze</td>
<td>Living within 50 m of a major roadway Average daily vehicle count &gt;= 10.000</td>
<td>OR: 1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Cesaroni G, 2008</td>
<td>9488 subjects (25–59 yrs) Rome</td>
<td>Rhinitis</td>
<td>Living within 50-100m of a major road</td>
<td>OR: 1.26 (1.03-1.54)</td>
</tr>
<tr>
<td>Shikowski T, 2005</td>
<td>4757 women (55 yrs) Germany</td>
<td>Cough</td>
<td>Living within 100m of a major road</td>
<td>OR: 1.24 (1.03-1.49)</td>
</tr>
<tr>
<td>Bayer-Oglesby L, 2006</td>
<td>8047 subjects Switzerland</td>
<td>Phlegm Wheezing with breathing problems (in never smokers)</td>
<td>Living within 20m of a major road</td>
<td>OR: 1.15 (1.00-1.31) 1.34 (1.00-1.79)</td>
</tr>
<tr>
<td>Mc Connell R, 2006</td>
<td>4762 schoolchildren (5-7 yrs) USA</td>
<td>Lifetime asthma Current asthma Wheeze</td>
<td>Living within 75 m of a major roadway</td>
<td>OR: 1.29 (1.01-1.86) 1.50 (1.16-1.95) 1.40 (1.09-1.78)</td>
</tr>
<tr>
<td>Gauderman WJ, 2007</td>
<td>3677 children (mean 10 yrs [SD 0.44]) USA</td>
<td>Deficit in 8-year growth of: FEV1 MMEF</td>
<td>Living within 500 m of a freeway (motorway)</td>
<td>~81 mL (~143 to ~18) ~127 mL/s, (~243 to ~11)</td>
</tr>
<tr>
<td>Kan H, 2007</td>
<td>15792 subjects (mean 54.2 yrs [SD 5.8]) USA</td>
<td>FEV1 reduction FVC reduction</td>
<td>Living within 150 m of a major roadway</td>
<td>-15.7 ml (-34.4 to 2.9) -24.2 ml (-46.2 to -2.3)</td>
</tr>
<tr>
<td>Forbes LJL, (2009)</td>
<td>56 727 adults England</td>
<td>FEV1 reduction in men FEV1 reduction in women</td>
<td>10 µg/m3 difference in NO₂</td>
<td>-30 ml (-42 to -17 ml) -16 ml (-24 to -7 ml)</td>
</tr>
</tbody>
</table>
(14) Most previous studies are conducted either in adults or children. One unique feature of this study is the wide age range. The authors may want to talk about some of their results in different age groups for a more direct comparison.

We understand not having been detailed in the original manuscript on these issues. Indeed, children (0-14) represent a very small proportion of our sample (5%), which doesn’t allow to conduct stratified analyses. Moreover, the age group variable was included in the logistic regression model in order to take into account the independent effects of age.

(15) The authors should dedicate a bit more space in the discussion to additional (non-geocoding) strengths and limitations of their analysis. One topic they should certainly mention is socioeconomic status, since it has often been shown to be a confounder or effect modifier in studies of proximity to traffic/air pollution. Additional comment on the apparent effect modification by gender is also warranted.

Following all reviewers’ suggestions, discussion section has been completely modified through adding more comments on strengths and limitations, potential confounders and sex-specific effect modification.

(16) The second part of the conclusion may be true, but I am not sure that it follows from the rest of the text.

We have modified this section

(17) The authors should also have a statement about human subjects procedures somewhere in the document. Are there any privacy concerns with the tight spatial focus of Figure 3?

Regarding the tight spatial focus of Figure 3, we have to notice that buildings in the study area are usually made of a large number of apartments so that it is not possible to identify subjects from the position of buildings. Moreover, Italian law did not request the approval of Ethical Committee at the time of the field survey. Furthermore, this survey was performed using a standard protocol, which already had passed the scrutiny of independent reviewers. In addition, the protocol was approved by an Internal Review Board within the Preventive Medicine Target Project of the Italian National Research Council. Participating subjects gave their consent to the study methods and to the use of their data for collective anonymous statistical analyses.

Reviewer’s report
Title: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health
Version: 1 Date: 31 August 2010
Reviewer: Shelley Green

Reviewer's report:
Review of EH 1568821879430283: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health

Major Compulsory Revisions:
General Review: This is an interesting paper which adds to the literature important information about the effects of living near a busy road on respiratory symptoms and lung function. The data collected in 1991-1993 included important information on lung function and allergies. The paper is fairly well written, but it needs some editing because the English language (not the first language of the authors, I presume) is not always clear or up to the standards of an English language journal. Please be consistent when indicating periods or commas in numbers.

The methods section does not clearly state which road or roads were considered busy roads for this study. It seems from the Figure 1 legend that the Tosco-Romagnola highway was the only busy road used in this analysis. If that is the case, it should be clearly stated in the Methods background section.

We realize not having gone into detail in the original manuscript on these issues. Following all reviewers’ suggestions, we have modified the text to better describe the study area: only one road (Tosco Romagnola) was considered in the study. The term “highway” was misleading. Authors removed this term from the text; the correct term is “main road”. Characteristics of Tosco Romagnola have been better described in method section.

The authors should include some details about the highway, such as the number of vehicles passing through each day.

We thank the reviewer for this suggestion. During the survey a traffic volume monitoring campaign was implemented: mean daily values was about 14700 vehicles/day measured in the period 07.00-21.00. These data have been added in the text.

Figure 3 makes it look like people are actually living on the highway. Are there homes right next to the highway?

As previously described, the term “highway” was misleading. We removed this term from the text; the correct term is “main road”, thus it is possible that homes are right next to the road. Characteristics of Tosco Romagnola have been better described in method section.

The authors should at least describe the orientation of the highway to the prevailing winds.

We thank the reviewer for this suggestion. Historical data on meteorological variables collected by Pisa International Airport report a prevailing wind direction parallel to the Tosco Romagnola road direction.

It would also be interesting to know whether the construction of the new highway between 1988 and 1991 had an effect on the exposure to air pollutants.
from the highway. If exposure was reduced, was there a difference in symptom reporting between the first and second surveys? This could be part of the discussion.

Following all reviewers’ suggestion, for the sake of clarity, section on description of the first survey was completely eliminated from the text. We decided to focus on the second survey because of the larger amount of available objective data. Details on the comparison between the two surveys are reported in Viegi et al. 1999 (Viegi G, Pedreschi M, Baldacci S, Chiaffi L, Pistelli F, Modena P, Vellutini M, Di Pede F, Carrozzi L: Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. Int J Tuberc Lung Dis 1999, 3:1034–1042; Baldacci S, Carrozzi L, Viegi G, Giuntini C. Assessment of Respiratory Effect of Air Pollution: Study design on general population samples. JEPTO 1997;16:77-83). Furthermore, as suggested by another reviewer we have planning longitudinal analyses to be reported in a subsequent paper.

Specific Comments:
Page 5, Background: The information about the air pollution in the three zones used in the first study (1985-1988) is probably not necessary. It would be more informative to give information about pollution near the Tosco-Romagnola highway before and during the second survey, since the current study focuses on that highway. Also, how did the construction of the new highway affect air pollution levels?

As already explained, section on description of the first survey was completely eliminated from the text. Pollutants measures during the second survey were so sparse that authors decided not to include them in the analyses. However, major details on the comparison between the two survey are reported in Viegi et al. 1999, showing that the levels of conventional pollutants were reduced probably because the heavy traffic (mainly trucks) was diverted from the zone of residence, since the new highway is far from the investigated zone, as above reported. (Viegi G, Pedreschi M, Baldacci S, Chiaffi L, Pistelli F, Modena P, Vellutini M, Di Pede F, Carrozzi L: Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. Int J Tuberc Lung Dis 1999, 3:1034–1042).

As previously described, the term “highway” for Tosco-Romagnola road was misleading. Authors removed this term from the text; the correct term is “main road.

Were there a total of 3866 subjects used in the second survey, or was that the number in the first survey? How were the study subjects selected?

Subjects enrolled in the second survey were 2841; indeed, 3866 subjects were those participating in the first one. As already described, for the sake of clarity, section on description of the first survey was completely eliminated from the text. Some details on sample selection have been added in the methods section.

Page 6: Was the total sample size for the current study 2841, or was it 3866, 2841 of which were investigated with the extended protocol? The authors state that the annual means of the air pollution measurements decreased between the two surveys. Where were these measurements made? Were they near the highway?
As above explained, 2841 was the total sample size for the current study in which an extended protocol was used. In addiction section on description of the first survey was completely eliminated from the text together with the pollutant concentrations related to Pisa south-east. Pollutants measures currently reported in the text are those referred to the monitoring station located in Cascina Municipality along the Tosco-Romagnola road. As previously described, the term “highway” was misleading. We removed this term from the text; the correct term is “main road”.

Page 6, Exposure assessment: Please define the “main road.” I assume you mean the Tosco-Romagnola highway. Can you give an estimate of the number of vehicles that pass by per day and the type of vehicles such as cars and trucks?

Characteristics of Tosco Romagnola have been better described in method section, including information on traffic volume (about 14700 vehicles/day range 07.00-21.00), as measured by an ad-hoc monitoring campaign performed during the epidemiological survey. We have no data about type of vehicles.

Also please specify whether the cars are powered by diesel or gasoline, or both fuels.

We thank reviewer for this suggestion, but we have no data on vehicles classification in the study area at the time of the survey, but historical data (1989-1992) of vehicles registration report the following values for the municipality of Pisa: 49% vehicles powered by gasoline, 25% by diesel, 6% by CNG (compressed natural gas) and 20% motorcycles (without specify the type of fuel).

Can you classify subjects as living upwind or downwind of the highway?

We thank the reviewer for this suggestion. Historical data on meteorological variables collected by Pisa International Airport report a prevailing wind direction parallel to the Tosco Romagnola road direction. Thus, we were not able to classify subjects upwind or downwind of the road.

You may describe “vectorial cartographical” as simply “vector” data.

We thank reviewer for this suggestion: “vector” data has been used.

What are civic numbers? Are they the same as street numbers in the United States (eg numbers on houses and commercial buildings?) For United States audiences you may refer to civic numbers as street numbers, if that is the case.

We understand that it is not easy to compare different situation: the term civic numbers was probably not correct, the right term can be “house numbers”, as suggested by other reviewers. The text has been modified.

Page 8: What does walking in “plain” mean? Do you mean on level ground?

We agree with the reviewer: the right term is on ground level. The text has been modified.

Please define FVC and VC.
FVC and VC have been defined in methods section

Please define “smoking habits” (eg. never, former, current, ETS exposed).

Following all reviewers’ suggestion, we added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including smoking habits.

Page 9: Please define airways obstruction more clearly. Do you mean that if the observed FEV1/FVC% was less than 70%, the subject was defined as having airways obstruction?

Airway obstruction was defined as having an observed FEV1/FVC% less than 70%

When describing the wheal, do you mean one or more wheal of at least 3mm or 5mm? In the last paragraph, what working exposure did you examine?

The text has been modified to better explain this topic. Positive subjects to skin prick tests (as atopy markers) were those characterized by one or more wheal with a mean diameter of at least 3mm (skin test_3mm pos) or 5mm (skin test_5mm pos), after subtracting the diameter of the negative control reaction. We added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including occupational exposure, defined to be or have been exposed to fumes, gases, dust or chemicals in working environments.

Please spell out OR.

The text has been modified.

Page 10: What work exposures examined?

As noticed by all reviewers, we added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including occupational exposure. It has been defined as to be or have been exposed to fumes, gases, dust or chemicals in working environments. In the modified text only the term ‘occupational exposure’ has been reported.

Page 11: Did you perform a trend test for any of the results reported in Table 4?

We had performed chi-square trend test, no significant results were observed.

Page 13: The “main road” should be specified here (Tosco-Romagnola highway), Characteristics of Tosco Romagnola road have been better described in method section.

What occupational exposure did you examine?

As above explained, we added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including occupational exposure. It has
been defined as to be exposed or have been exposed to fumes, gases, dust or chemicals in working environments.

Page 14: It would be informative to mention the geographic locations of the previous studies documented in the discussion, since air pollution levels vary across countries and cities.

The geographic locations have been added.

Page 17: What do you mean when you say you do not adopt a metric scheme for civic numbers? Were you able to match the civic numbers in the subjects’ addresses with locations on the map you used for geocoding? I think the answer is “yes” but you should make it very clear, because this is a strength of your study. (you state “exact correspondence of civic numbers to related buildings).”

We thank the reviewer for her constructive comments. Since the sentence “adopt a metric scheme for civic numbers” was misleading, we decided to modify it. Geographical strengths (high precision) of the study have been better described in methods and discussion sections.

Minor Essential Revisions:
Table 1: What is working exposure?

In the modified text only the term ‘occupational exposure’ has been reported.
As above explained, we added a new paragraph completely dedicated to potential confounders and the large amount of data collected through questionnaire, including occupational exposure. It has been defined as to be or have been exposed to fumes, gases, dust or chemicals in working environments.

Tables 2 and 3 and 4: In the heading you should indicate “Distance of residence to the highway”.

Tables have been modified

Table 3: Add the words “bronchial reactivity” to slope_log.

The words “bronchial reactivity” has been added

Discretionary Revisions:
Perform separate analyses for subjects living upwind or downwind of the highway. If only one highway was used to determine exposure, it would be interesting to perform separate analyses for subjects living upwind or downwind of the highway. Actual exposure may be substantially different for those living on different sides of the highway.

We thank the reviewer for this suggestion. Historical data on meteorological variables collected by Pisa International Airport report a prevailing wind direction parallel to the Tosco Romagnola road direction. Thus, we are not able to classify subjects upwind or downwind of the road.
Reviewers report
Title: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health
Version: 1 Date: 27 August 2010
Reviewer: Joachim Heinrich

Reviewer's report:
Nuvolone D et al
The study by Nuvolone et al. analysed the association between living close to major roads and respiratory health in the general population in northern Italy. The strength of the study is that distances to a major road has derived from GIS, and the rich data set, which was gathered by detailed lung function measurements, skin prick tests and further blood tests for IgE measurements. Unfortunately the methodology including the statistical analyses is insufficient. Thus it is questionable whether the study substantially adds to the current knowledge. The major shortcomings of the study will be addressed below.

Major
The statistical analysis plan obviously focussed to study sex-specific associations, although this question was neither mentioned as a major aim nor was it discussed. Also the presentation of the key findings followed the sex specific question, which was never justified why long term exposure to ambient traffic related air pollutants should have a different effect in men and women. There is no consistent finding of potential effects of air pollution exposure on the outcome of interest between men and women. This causes some scepticism. The question is whether the sex specific effect was an a priori assumption before having looked at the data or whether this decision on sex-specific analysis was made after having seen that there is no overall health impact of the traffic related pollutants.

We decided to give sex-specific results for two main reasons:
1. Some authors highlighted that the dimensional, immunological and hormonal factors interact to different degrees and direction with environmental exposures experienced by males and females; the authors of these reviews suggest to use the stratification by sex, instead of standardization, in epidemiological studies. (Kauffmann, Eur Respir Mon 2000, Becklake, Eur Respir Mon 2003; Clogherty, Envir Health Perspect 2010).
2. preliminary analyses on potential confounders (age, education, occupational exposure and so on) reported a clear diversification between gender (table 1). Following reviewer’s suggestion, authors have better underlined these aspects in the text

It is not acceptable, that continous outcomes such as the log slope for BHR testing was just dichotomized and a lot of information of the continuous variable was not used. This is more or less the case as well for the IgE data.

We had already reported in table 4 (ex 3) results from analyses of variance for BHR and IgE, adjusting for age, smoking habits and predicted % FEV1 (only for BHR). No significant results were found.
Following reviewer’s comments, we have also fitted multiple linear regression model, using the same set of adjusting variables as in logistic regression analysis. Similar results have been
observed, thus no modification has been put in the results reported in the text, as suggested by the other four reviewers.

The age of the study population remained hidden. It is unknown whether also children were included in the analysis or not. This is not acceptable in particular when outcomes such as COPD and COPD related outcomes were used, which were not present in childhood.

Following reviewer’s suggestion, average age by gender (and range) has been added in the text. Indeed, children (0-14) represent a very small proportion of our sample (5%), not allowing to carry out stratified analyses. We have repeated the analyses excluding children: similar results have been observed. For these reasons and to be consistent with our previous articles, all the investigated subjects have been included in the analyses.

Moreover, recent studies showed that childhood respiratory infections can have a negative impact on the respiratory lung function into adulthood (20-44-yrs old) but also affect development and persistence of adult respiratory morbidity (Dharmage SC, ERJ 2009); this association was confirmed also in younger adults (18-20 yrs), whose lung function abnormalities were associated with respiratory infection which required hospitalization in infancy (Korppi M, Pediatr Pulmonol. 2004). Since lung development is nearly complete by age 18 years, an individual with a deficit at this time will probably continue to have less than healthy lung function for the remainder of his or her life. For these reasons, we think it is important to consider also this age group in the analyses regarding COPD and COPD related outcomes.

The exclusion of subjects who are living farther away than 800 m to a major road is not convincingly justified. The reader would like to see the entire data set of the study.

Following all reviewers’ suggestion, we have modified the text to better describe the study area. Characteristics of Tosco Romagnola road, which have led us to decide to exclude subjects living farther away from 800m, have been better described in methods section: in particular, this choice was done to minimize the effects of other air pollution sources (industries, other main roads), mainly in the western side of the Tosco-Romagnola road; the 800m cut–off permitted to exclude also the more rural area of the central-eastern side, characterized by different kind of buildings (villas, isolated houses) and by different socio-economics status. It is important to underline that for the central and eastern side of the road more than 90% of our sample lived within 800m of the road.

Minor
Abstract
The age of the study should be given, in addition 95% CI needs to be added to the OR and also whether the given OR were adjusted or not.

95% CI and adjustment process were added

The referenced literature is not complete and not up to date. The selection criteria for the referenced literature remain obscure. The presentation of the data does not follow the aim of the study. In addition, the age of the study subjects were not mentioned at all.
Following all reviewers’ suggestion, the discussion section has been completely reorganized, updating references, adding more comments on study advantages/disadvantages and average age by gender (and range) has been added in the text.

Method’s background
1st sentence: This sentence is referring to a “longitudinal epidemiological survey”, while I would consider two repeated cross-sectional surveys not as a longitudinal study. Since no data were used from the first survey in the year 1985-1988 all information on this study needs to be removed from the manuscript.

We thank the reviewer for this suggestion and decided to eliminate any comments on the first survey and to focus on the second survey (1991-93).

Exposure assessment, p. 6:
What was the definition for a main road? Please provide information on traffic volume. In addition to the simple distance to a major road other exposure metrics could also have been developed such as road lengths of main roads of a certain buffer or road lengths of minor roads within the three different buffer zones.

We thank the reviewer for this suggestion; as above noticed, characteristics of Tosco Romagnola road have been better described. As added in discussion section we faced with the problem of availability of input data to implement a more sophisticated approach than the distance-based method. Considering that the study area has typical characteristics of a suburban/rural area with sparse buildings, presence of very small streets and absence of industrial sources, Tosco-Romagnola road has the main role in air pollutants emission. Thus, we believe that the distance approach is useful for assessment of a potential health hazard due to environmental pollution. As regards traffic volume along the Tosco Romagnola road, during the epidemiological survey a traffic volume monitoring campaign was implemented: mean daily values was about 14700 vehicles/day measured in the period 07.00-21.00. These data have been added in the text.

Statistical analysis, p. 8:
A reference should be given how the percent predicted lung function values were calculated.

Following reviewer’s comment, a reference has been added.

Discussion, p. 13 ff:
My guess would be that this manuscript used only data from adults. Therefore all the referenced studies with children need to be removed. However, if also data from children were included in the manuscript, then the tables need to be completely reorganised showing the effect restricted to childhood.

As above explained, the study is a general population study, consequently we think it an added value for this paper. As requested by the reviewer, we have considered this topic: children (0-14) represent a small proportion of our sample (5%), which didn’t allow to carry out stratified analyses. We have repeated analyses excluding children: similar results have been observed; for these reasons and to be consistent with our previous articles, all the investigated subjects have been included in the analyses. In order to answer to reviewer’s request, the less significant references on
children have been removed. However, as highlighted by other authors (Lindgren A, Stroh E, Montnémery P, Nihlén U, Jakobsson K, Axmon A. Traffic-related air pollution associated with prevalence of asthma and COPD/chronic bronchitis. A cross-sectional study in Southern Sweden. International Journal of Health Geographics 2009, 8:2), studies on adults are very few, so that it is very difficult to compare our results with others without using the results of studies with children.

What is completely entirely unacceptable is that the gender specific effects which could be considered as the key message of the entire paper were not discussed with one single sentence.

As above mentioned, following reviewer’s suggestion, authors have better underlined these aspects in the text.

Conclusions, p. 18:
The first sentence is saying that both subjective and objective methods for the exposure assessment was used, but no data on subjective exposure assessment were shown in the tables or were described in the text.

The sentence referred to subjective (questionnaire) and objective (lung function and allergological test) methods used to assess respiratory troubles. It has been better described in conclusion section.

Table 1, p. 25:
Passive smoking is defined by inhalation of tobacco smoke by a non smoker. Thus, the numbers need to be referred to the non smoking population.

We agree with the reviewer, but we think that it is important to not reduce the analysis only on non smokers because the passive smoking could be an important risk factors also for active smokers as recently shown by Piccardo et al. (Environ Health, 2010), who found that during indoor smoking, ETS contribution to total daily benzo(a)pyrene dose of the same smoker, may be not negligible. Therefore they suggested that both active and passive smoking exposures should be considered in studies about health of active smokers.

However, the independent effects of active and passive smoking were considered in the logistic regression analysis.

The label ‘working exposure’ needs an explanation.

We added a new paragraph completely dedicated to potential confounders and the great amount of data collected trough questionnaire, including occupational exposure. It has been defined as to be or have been exposed to fumes, gases, dust or chemicals in working environments.

Reviewer’s report
Title: GIS and Environmental Epidemiology: spatial analysis of the effects of traffic-related air pollution on population respiratory health
Version: 1 Date: 9 September 2010
Reviewer: Giulia Cesaroni

Reviewer’s report:
This is an interesting paper on traffic exposure, assessed using GIS, and respiratory health. The dataset is very rich, and the subject is important. I think that this article is relevant in the field, but that can be considerably
improved.

Major points

Abstract

Since the abstract is the part which will be read most, I would suggest some improvements.

Few suggestions:
- Use GIS as acronym of the same thing in both abstract and text (I prefer GIS for Geographical Information System instead of Science)
- Specify the three levels of exposure (<100, 100-250, 250-800)
- The word “control” can be misleading and should be replaced with “unexposed”
- Highlight the richness of information available (FEV1, DLCO, FVC, etc…) in the abstract’s method section.
- The authors do not need to specify that they performed a sensitivity analysis on long term residents here.

We thank the reviewer for her constructive comments. All reviewer’s suggestions have been applied

Main Text

Methods

1. Page 5. Since in this paper the authors use the 1991-93 survey, it should be described in more depth, and more than the first survey

Following all reviewers’ suggestion, we decided to eliminate any comments on the first survey and to focus on the second survey (1991-93). We have rewritten this section through adding more information on study area, Tosco Romagnola road and study design.

2. Is the second survey on subjects aged 5-90 years? If so, it could be better to restrict the study to adult population (>17yrs). In this case the socio-demographic characteristics presented in Table 1 would be much understandable (for example education has different meaning according to age), and possible confounders such as working exposure or smoking could have the same meaning in all study population. On the other hand, if there is a specific interest on younger population, the analysis should be stratified according to age group, because it doesn’t make sense to collapse children and elderly subjects, and adjustment for age is not a solution of the problem.

The study is a general population study, consequently we think it is an added value for this paper to show figures concerning the entire sample. As requested by the reviewer, the authors have considered this topic: children (0-14) represent a small proportion of our sample (5%), which didn’t allow to carry out stratified analyses. We have repeated analyses excluding children: similar results have been observed. For these reasons and to be consistent with our previous articles, all the investigated subjects have been included in the analyses.

3. Exposure assessment. Please, give a definition of main road. It is not clear from the methods’ section if it is only the Tosco Romagnola highway. Have the authors got a measure of traffic counts on the main road? Is the study population exposed to high traffic even from other streets? The authors could describe it
As noticed by all reviewers, the term “highway” was misleading. Authors removed this term from the text; the correct term is “main road”. Characteristics of Tosco Romagnola road have been better described in method section.

Considering that the study area has typical characteristics of a suburban/rural area with sparse buildings, presence of very small streets and absence of industrial sources, Tosco-Romagnola road has the main role in air pollutants emission.

As regards traffic volume along the Tosco Romagnola road, during the epidemiological survey a traffic volume monitoring campaign was implemented: mean daily values was about 14700 vehicles/day measured in the period 07.00-21.00. These data have been added in the text. As we have added data on traffic volumes, we have not used TeleAtlas classification of roads.

Give here detail of Geocoding procedure instead of writing it in the discussion section.

Following reviewer’s suggestion, details of geocoding procedure has been given here.

4. Page 9: Potential confounders. The authors treated all the variables as confounders. Are the authors sure they are not effect modifiers? In some works for example smoking habit modified the effect of exposure to traffic on health. In this case it would be not appropriate to adjust.

We have investigated this topic: the presence of effect modifications has been assessed by introducing interaction terms in models. Homogeneity of coefficients across categories of various factors was evaluated using a likelihood ratio test ($\chi^2$). No effect modifiers have been observed.

5. The authors stratify the analysis by sex. Please give a reason for that.

We decided to give sex-specific results for two main reasons:
1. Some reviewers highlighted that the dimensional, immunological and hormonal factors interact to different degrees and direction with environmental exposures experienced by males and females; the authors of these reviewers suggest to use the stratification by sex, instead of standardization, in epidemiological studies. (Kauffmann, Eur Respir Mon 2000, Becklake, Eur Respir Mon 2003; Clogherty, Envr Health Perspect 2010).
2. preliminary analyses on potential confounders (age, education, occupational exposure and so on) reported a clear diversification between genders (table 1). Following reviewer’s suggestion, we have better underlined these aspects in the text.

Results

Even if this Journal allows to have more tables than usual I think that more concise results could help in the reading.

I suggest:
1. to have 1 figure with all the three you produced (Fig 1 A/B/C)

We have tried to join together the three figures, but, for sake of clarity, we prefer to leave three different figures, as they provide different information.

2. to avoid redundancies in the text (you do not need to repeat OR and 95%CIs of the tables)
As requested by other reviewers, 95% CI and OR have been eliminated from the text.

3. to write the effect of confounders

Following reviewer’s suggestion, a short comment on this topic has been added.

4. to eliminate table 6 (figures are already in tables 3-4)

We agree with the reviewer, table 6 has been eliminated.

5. to make table 1 more informative adding a column with the % of highly Exposed

Expanded the request of the reviewer, a new table (table 2) on distribution of potential confounders among the distance classes has been added.

Discussion

Since the results of the study are reported by sex and that the results are different in men and women, the discussion can be improved if these differences are highlighted and interpreted. I would discuss also the unexpected results (i.e. Table 5 FEV1/FVC%<70% and FEV1/VC%<70% for males) and what they imply in terms of interpretation.

Following all reviewers’ suggestion, discussion section has been completely reorganized. With regard to the unexpected results, as shown in table 2, the intermediate exposure class (100-250) presents high values for some confounding factors; even if estimates are adjusted for these factors, they still probably could have some residual influences. In addition a few factors, unconsidered in the present analyses, might have influenced these results: for example, subjects living within 100-250m have an higher prevalence of childhood respiratory troubles (chest cold, pertussis and bronchitis); in a previous study we showed that subjects with childhood respiratory troubles had the lowest lung function values regardless of smoking habits (Paoletti P, Prediletto R, Carrozzi L, Viegi G, Di Ped F, Carmignani G, Mammini U, Giuntini C, Lebowitz MD. Effects of childhood and adolescence-adulthood respiratory infections in a general population. Eur Respir J 1989;2:428-436).

If the authors restrict the age of the study population it is easier to discuss and compare their results with other studies.

As above explained, the study is a general population study, consequently we think it an added value for this paper. As above reported, we have repeated analyses excluding children: similar results have been observed. For the sake of completeness, all the investigated subjects have been included in the analyses.

Add a paragraph on limitations and discuss how they could influence the findings Issue of residual confounding should be raised.

Following all reviewers’ suggestion, discussion section has been completely reorganized through adding strengths and limitations of the study.
Minor points

Background
1. In the background Pope is cited (reference 4), but it is a paper on CVD. Why do not authors cite a paper (written by the same group) on respiratory health?

We apologize for this mistake: reference has been changed.

2. Spell out GIS (for the first time)

GIS has been spelled out.

3. Reference 26 (Briggs et al) I think it is about LUR models and not dispersion models.

We thank the reviewer for her comments: text has been modified

Methods
4. I suggest to change the heading “Background” in method section with “Setting and Study Population”

Text has been modified.

5. p. 7 use unexposed instead of controls.

Text has been modified.

6. Health outcome assessment. Can authors include a reference for the questionnaire?

The reference has been added in the text.

7. Page 9 “OR were adjusted for the effect of sex….” Authors can specify that they use stratification for sex, instead of saying simply that they adjust.

Text has been modified.

Results
1. Be careful with /./ for decimals. For distances is not useful to have the decimals.

Text has been modified

2. Page 11. I suggest to delete “(borderline significance)” in the last row.

Text has been modified

3. Table 1 I suggest to add those without education with primary school.
The variable has been reclassified in three groups, by merging individuals without education with those with primary school education.