

## **Author's response to reviews**

**Title:** Respiratory symptoms in children living near busy roads and their relationship to car and truck traffic: Results of an Italian multicenter study (SIDRIA 2)

### **Authors:**

Giovanna Berti ([g.ber ti@arpa.piemonte.it](mailto:g.ber ti@arpa.piemonte.it))  
Enrica Migliore ([enrica.migliore@cpo.it](mailto:enrica.migliore@cpo.it))  
Claudia Galassi ([claudia.galassi@cpo.it](mailto:claudia.galassi@cpo.it))  
Neil Pearce ([n.e.pearce@massey.ac.nz](mailto:n.e.pearce@massey.ac.nz))  
Francesco Forastiere ([forastiere@asplazio.it](mailto:forastiere@asplazio.it))  
Lucio Armenio ([l.armenio@pediatria3.uniba.it](mailto:l.armenio@pediatria3.uniba.it))  
Annibale Biggeri ([abiggeri@ds.unifi.it](mailto:abiggeri@ds.unifi.it))  
Luigi Bisanti ([lbisanti@asl.milano.it](mailto:lbisanti@asl.milano.it))  
Massimiliano Bugiani ([m.bugiani@aslto4.it](mailto:m.bugiani@aslto4.it))  
Ennio Cadum ([e.cadum@arpa.piemonte.it](mailto:e.cadum@arpa.piemonte.it))  
Elisabetta Chellini ([e.chellini1@cspo.it](mailto:e.chellini1@cspo.it))  
Valerio Dell'Orco ([valerio.dellorco@tiscali.it](mailto:valerio.dellorco@tiscali.it))  
Gabriele Giannella ([gabriele.giannella@aslmn.it](mailto:gabriele.giannella@aslmn.it))  
Piersante Sestini ([sestini@unisi.it](mailto:sestini@unisi.it))  
Giuseppe Corbo ([gmcorbo@yahoo.com](mailto:gmcorbo@yahoo.com))  
Riccardo Pistelli ([pneumologia@h-columbus.it](mailto:pneumologia@h-columbus.it))  
Giovanni Viegi ([vi egig@ifc.cnr.it](mailto:vi egig@ifc.cnr.it))  
Giovannino Ciccone ([gianni.ciccone@cpo.it](mailto:gianni.ciccone@cpo.it))  
SIDRIA 2 Collaborative Group ([claudia.galassi@cpo.it](mailto:claudia.galassi@cpo.it))

**Version:** 3 **Date:** 1 December 2008

**Author's response to reviews:** see over



UNIVERSITA' DI TORINO

DIPARTIMENTO DI SCIENZE BIOMEDICHE  
E ONCOLOGIA UMANA

Sezione di Epidemiologia dei Tumori  
CPO-Centro di riferimento per l'Epidemiologia  
e la Prevenzione Oncologica in Piemonte

**Enrica Migliore**

**Cancer Epidemiology Unit**

Department of Biomedical Sciences and Oncology  
University of Turin

Via Santena 7

10126 Torino

Italy

Tel: +390116336856

Fax: +390116334664

e-mail: [enrica.migliore@cpo.it](mailto:enrica.migliore@cpo.it)

Torino, 1 December 2008

Environmental Health  
BioMed Central Ltd  
Middlesex House  
34-42 Cleveland Street  
London W1T 4LB, UK

Manuscript number: 3145967701926989

Dear Dr Grandjean,

Please find attached a revised version of the manuscript entitled "Respiratory symptoms in children living near busy roads and their relationship to car and truck traffic: Results of an Italian multicenter study (SIDRIA 2)".

We would like to thank the reviewers for their valuable comments and constructive criticisms. We have revised the manuscript in the light of their suggestions. A detailed response to the reviewers' comments is also attached.

With regard to one of the points raised by both reviewers (evaluation of the presence of a possible response bias), several additional analyses have been conducted. We reported and discussed in depth the results obtained in a separate manuscript, that we are sending as a confidential draft and that will soon be ready for submission to your journal. We have added several comments on this issue in the present paper, also referring to the manuscript in preparation.

Thank you very much for your attention and your consideration.

Yours sincerely,

Enrica Migliore

**Reviewer:** Bert Brunekreef

**This is in most ways a repeat study of the Ciccone OEM paper published in 1998. What this study adds is more specificity on cars and trucks. The main issue with questionnaire based studies like this is the potential for response bias. The recent papers by Kuehni and Piro – which the authors show themselves to be keenly aware of – make clear that this is a very real concern. The authors now restrict themselves to reporting some associations between self reported traffic densities and objective traffic counts and/or pollution measurements, but that is not enough. The question is whether traffic densities are differently reported by parents of kids with and without symptoms. The authors should as a minimum do an analysis similar to the one performed by Kuehni, who identified cases and controls living in the same street (post code area) and then showed that parents of case children systematically reported higher traffic densities for the same streets. From their discussion in the 3d to last paragraph it seems that the authors should have the data to do so.**

According to this useful suggestion of both the reviewers, we performed several analyses in order to evaluate the presence of a possible response bias. We reported and discussed in depth the results in a separate manuscript, that we are sending as a confidential draft and that will soon be ready for submission. We added several comments on this issue in the present paper also referring to the manuscript in preparation.

**What's missing is a basic cross tabulation of frequencies of car and truck traffic densities for the whole population.**

We added this information in the appendix (Table 2).

**Another issue is the use of complex endpoints ('current asthma symptoms' and 'persistent cough or phlegm'). It would be good in addition to have one table showing the associations with the key individual ISAAC symptom variables, if only for comparison with the literature.**

We added this information in the appendix (Table 3), including also a separate analysis for severe and light asthmatic symptoms, and for symptoms of cough or phlegm of different duration. We also better clarify the definition of the endpoints in the text, according to the request of the other reviewer.

**The authors chose not to use the self-completed questionnaire from the 13-14 yr olds. That seems odd, because it would add strength to the findings if they were able to show that similar associations are observed when exposure and symptoms are reported by the adolescents themselves rather than by their parents. I strongly recommend to add an analysis of these data to the paper.**

We did not collect information regarding exposure from the adolescents although they reported respiratory symptoms. We previously observed (Renzoni et al, 1999) that there is a higher sensitivity among adolescents in the report of respiratory symptoms when compared to what reported by their parents; in particular, prevalence of asthma symptoms is significantly higher when the information is reported by adolescents themselves. The same result was observed in the second phase of the study. Since for the younger age-group only information reported by parents was available, for reasons of consistency and comparability between age groups, we based the current analyses on the parental questionnaires for both age-groups.

Nonetheless, we performed an overall sensitivity analysis in which, for the older age group, we used the information on symptoms reported by adolescents, as it was done in the previous paper (Ciccone 1998); these results have been reported in the appendix (Table 4).

**Again for reasons of comparability with the literature, it would help if the authors provided the exact wording of the questions on traffic density that they used.**

We added the wording on the traffic questions in the appendix (Table 1).

**It is unclear why effect modification was only studied for the truck associations, not the car associations.**

We decide to explore effect modification for the indicator of traffic exposure for which we found the strongest associations with symptoms. However, we repeated the analysis for the indicator of car traffic, and results are now presented in the appendix (Figure 1).

**Paragraph 4 of the discussion can be deleted, it is too unspecific to be of use here.**

We deleted paragraph 4.

**The point in para 5 of the discussion about diesel cars is well taken. No doubt the authors can have access to data on percentage of diesel cars in Italy that they can quote to support their assertions**

We added a reference for the Italian context: Ente per le Nuove tecnologie, l'Energia e l'Ambiente (ENEA). Rapporto energia e ambiente. ENEA, Roma, 2005.

**Were the effect modifications shown in figure 1 significant?**

We have reported the results for the interaction tests. In Figure 1 we also added the results for other possible effect modifiers. We explored more deeply the data for effect modification, including all the variables used as potential confounders in the main models. However, in order to limit the number of statistical comparisons and to improve the comparability with the literature, we used only the two basic endpoints, "asthma symptoms" and "cough or phlegm".

## **Reviewer's report**

**Reviewer:** Josep Anto

### **MAJOR COMPULSORY REVISIONS**

**1. Page 4, 2nd par, last sentence. The authors justify the study on the fact that in its previous paper (ref 18) it was not possible to assess the independent effects of car and truck traffic since in that (earlier) study the information was not available. However the article in ref 18 includes information of lorry traffic and buses lines in several tables, so the justification of this new study needs to be clarified. In other parts of this revision there are other comments about comparability between the present manuscript and the article in ref 18. Since both studies included very similar populations in almost the same areas, it important that the authors make an effort to clarify the links between both papers.**

SIDRIA-2 was conducted in most of the areas of SIDRIA-1 on purpose since we intended to evaluate time differences in prevalence, according to ISAAC protocol. However, in the second survey centres in Southern Italy were added (representing around 15% of the whole sample) so that the two samples are not equal.

In the first phase of the study we did not include a specific question on car traffic in the street of residence, since we were specifically interested on the health effects of diesel exhausts (and therefore we asked the frequency of passage of both trucks and busses). However, since the proportion of cars powered by diesel has increased a lot in the last years and associations between car counts and respiratory symptoms have been reported in the literature, the question on car traffic was introduced in the second phase of SIDRIA (and the question on busses was dropped).

Another relevant difference between the two questionnaires is that in the first phase the

traffic questions were limited to people living in houses with windows facing the street, whereas in the second phase we asked these questions to all subjects in the sample.

**2. Page 6, pars 2nd and 3rd. Stratification by type of symptoms is a main analytical strategy in the present study yet the way that symptoms were grouped remains unclear. For current asthma symptoms, which to a large extent are contributed by wheezing, presence of a cold is not mentioned as an exclusion criteria (as it is for nocturnal cough). The composite definition of “persistent cough or phlegm” is difficult to read and the second part of the definition seems to involve the joint presence of its three symptoms (nasal discharge, nasal congestion and nocturnal cough). The recall periods of the definition of “persistent cough or phlegm” are given in a way that would be hard to answer in a questionnaire. Providing the exact wording of questions may help. In addition, including nocturnal cough among “bronchitis type symptoms” instead of among “asthma like symptoms” is arguable. There are other potentially relevant limitations on the way that respiratory symptoms are approached. Symptoms are labelled as “current asthma symptoms” and “persistent cough or phlegm”, but in both cases recall period seems to refer only to the last 12 months and so, the distinct labelling is misleading. The definitions of “current asthma symptoms” and “persistent cough or phlegm” need to be clearer and appropriate references supporting the adopted definitions should be provided.**

We acknowledge that the definition of the subgroups of symptoms reported in the text was unclear.

The rationale for using such composite groups is that there is a well known strong correlation between different asthmatic symptoms, and also between asthmatic symptoms and symptoms of cough and phlegm. We therefore decide to define two different subgroups: one characterized by typical asthmatic symptoms and one characterized by productive symptoms (of the lower or of the upper respiratory tract). In this last group, we included also the positive answers to the single question that identified “sinusitis-like symptoms” (that involve the joint presence of nasal discharge, nasal congestion and nocturnal cough for more than 7 days, in the last 12 months, apart from colds), given the possible associations between traffic exposure and infections of the upper respiratory tract (Reinert P et al. Recurrent upper respiratory tract infections and otitis in children. *Rev Prat.* 2007 Oct 31;57(16):1767-73.). However, for comparability with other studies, we re-analysed the data including only symptoms of cough or phlegm, and we reported these results in the revised paper. The findings are substantially unchanged compared to the previous ones.

The symptom of “night cough” was the ISAAC question related to nocturnal dry cough (in last 12 months, and apart from colds). This last question was in fact included only among asthmatic symptoms, although this was erroneously not mentioned in the text.

As also suggested by the other reviewer, we added in appendix the ORs for the associations observed for the basic asthma symptoms as well as those for severe and light asthma symptoms. We also reported in the appendix the results of the analyses performed for symptoms of cough or phlegm of different duration (Table 3).

**3. Exposure to air pollution to cars and trucks is assessed through parent’s answers to a questionnaire. Validity and reliability of this approach should be considered in more detail including appropriate references if available. Though there is available data from Turin that allows for a small validation exercise, this information is only provided in the discussion in a superficial way. It would be useful to have the data from Turin included in the analysis with stratification according to type of traffic since this was the main aim of the study. A major concern with both respiratory outcomes and traffic exposure being assessed by questionnaire is the presence of recall bias. Since the study was conducted in schools the authors could look to those living in the same streets and to assess**

**whether the presence of respiratory symptoms is associated to a reporting a higher traffic density both for cars and trucks. The large sample size and the school clustered design of SIDRIA 2 may provide an interesting opportunity to approach such a relevant issue.**

According to this useful suggestion of both the reviewers, we performed several analyses in order to evaluate the presence of a possible response bias. We reported and discussed in depth the results in a separate manuscript, that we are sending as a confidential draft and that will soon be ready for submission. We added several comments on this issue in the present paper also referring to the manuscript in preparation.

#### MINOR ESSENTIAL REVIEWS

1. **Pag 3, 3rd line of results, “can” should be “car”.** Corrected. Thanks.
2. **Page 3, last sentence is unclear.** We modified the sentence
3. **Ref 31. “Jama” should be “JAMA”.** Corrected. Thanks.
4. **Table 2 and other sections. Parental atopy should most likely correspond to parental allergy.** We modify the label as “Parental asthma or allergies”.

#### DISCRETIONARY REVISIONS

**1. Severity of symptoms is not taken into account but it may well be the case that the larger odds ratios for “persistent cough and phlegm” are due to both definitions “current asthma symptoms” and “persistent cough or phlegm” involving different severity profiles. The authors could have stratified “current asthma symptoms” according to severity as they did in a previous paper (ref 18).** We add in appendix an analysis showing separate results for light and severe asthma symptoms, and for symptoms of cough or phlegm of different duration (Table 3).

**2. In addition to previous comments about traffic assessment there are other relevant limitations that may have biased the results. Since children in the age range included in the study are likely to attend schools in the vicinity of their residence one may expect, at least in the metropolitan areas, both exposures to be positively correlated. If the later would be true those who are exposed to either low traffic or high traffic streets both at home and at the school would provide two more extreme groups of exposure and more room to approach the study question. Other relevant limitations include the lack of information about residential history, duration of residence at the current address, flat altitude if living in an apartment or ventilation characteristics. Information about residential changes due to respiratory problems could also be very useful if available. The discussion provided about misclassification of exposure is too self-protective and a more balanced analysis of different consequences (including recall bias) should be provided.**

The absence of information on traffic density around the school has been added to the limits of our study. Since we collected some information on residential history and on flat altitude, we repeated all the analyses including in the regression models two variables: the flat of the apartment and the change of residence (not necessarily related to respiratory problems). These variables were excluded in the first analyses because they did not act as confounders, but we agree that their inclusion in the final analyses is reasonable.

**3. One of the strengths of the study is the wide geographical distribution of the population within Italy. In the previous report from SIDRIA 1 (ref 18) the authors reported that after stratification by type of area, most of the observed associations did only remain in the metropolitan areas (as compared to the rest of urban and non-urban areas.) One would expect to have the same geographical pattern in the present study. The information provided in Figure 1 does not answer this question. We added in Figure 1 the associations observed separately for metropolitan and non-metropolitan areas.**

**4. Regarding the stronger associations in females it would be useful to know whether such pattern was present for both age groups.**

A similar pattern was observed for both age groups. We added this information in the text.