Reviewer’s report

Title: Particulate matter air pollution and respiratory symptoms in subjects having either asthma or chronic obstructive pulmonary disease: a European multicentre panel study

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Reviewer: Ute Kraus

Reviewer’s report:

This manuscript by Karakatsani and colleagues examines the association between different air pollution measures and respiratory symptoms in patients with asthma and/or COPD. The data came from the RUPIOH study, a well-designed EU-funded multicenter study in which air pollution exposure was extensively assessed. In addition, the authors used data on gaseous pollutants collected from existing national monitoring networks.

In general, the topic is of high scientific interest. However, the manuscript in its current form raises several questions since a lot of information is missing. For example, the authors did not describe how they performed the meta-analysis in the statistical analyses section. Furthermore, there are several non-mentioned preventive associations which needed to be discussed.

(1) Major compulsory Revisions

(1.1) In general

Please explain all your abbreviations when you use it for the first time (e.g. COPD, QA/QC). In addition, the authors should then stick exactly to these abbreviations throughout the manuscript (terms that were used: e.g. particles less than 2.5 µm (PM2.5), fine (<2.5 µm) particles, coarse (2.5-10 µm) particles, coarse particles, PM10-2.5, coarse particle mass (PM10-2.5) PMcoarse).

It would be easier for the reader if the author shorten their sentences.

The authors set emphasize on the effects of coarse particles. However, they also analyses associations between symptoms and gaseous pollutants which needed to be mentioned in every section.

(1.2) Abstract

Background:
- The description on the RUPIOH study corresponds to the methods section. A clear statement about the background is missing.

Methods:
- Please add information on the statistical model making clear that you performed
a city-specific analysis and a meta-analysis.
- The last sentence describes the objective of the study and does not fit in the method section.
- Please note that you analysed 24-hour means of air pollution measures.
- The information that you also analysed associations with gaseous pollutants needed to be mentioned here as you report the results on Ozone and NO2 in the results section.

Results:
- Please add information on confidence intervals. To state only the magnitude of the increase does not provide enough information on the association.
- Please give a definition of “lag 1” or better write “lag of one day”.
- The authors need to state also their preventive results.

(1.3) Background
- Page 5: “In this paper, we report the association…” Please state that you also analysed associations with gaseous pollutants.

(1.4) Methods
Study design
- Last sentence: Please clarify the meaning of “staged entry of the subjects”. Did you use a fictive date for each participant or the real date the participants started to fill out the diaries?

Study population:
- You stated that participants were aged 35 or more. However, according to Table 1 there is at least one person aged 33 in Athens. Please clarify!

Symptom diary:
- “…limitation in daily life activities…” Please clarify the meaning of the words in brackets. The reader does not understand it until you refer to Table 2 in the results section. In addition, please give an example for vigorous and moderate activities.
- Did you include every person regardless of how many diary entries were made? Did you exclude diary entries when participants left the study area during the measurement period?

Air pollution exposure
- Please write more precisely on which basis you obtained the concentrations of your pollution measures. Actually, for PNC and the gaseous pollutants you did not state that you obtained 24-hour means. Were the 24-hour means calculated from 1-hour/half-hour means? If yes, how many 1-hour means had to be present for valid 24-hour means?
- How did you handle missing values?
- The authors state that data on concentrations of SO2, NO and CO were also collected. This information can be skipped as no results on these measures are reported.

Confounder data
- Do you think symptoms of a cold or flu could be a confounder, too?

QA/QC
- Please write QA/QC out as you did not define the abbreviation before.
- Did you calibrate the CPC at least once a year? Did you perform comparisons between the cities?

Statistical analysis
- In the symptom diary section you wrote symptoms were rated as (0) absent, (1) slight, (2) moderate/severe. Which one is correct?
- Model selection: Did you force same-day and previous-day mean daily temperature simultaneously into the models or did you test which one led to a better model fit. Please clarify!
- Which lag of relative humidity did you include in the models?
- In Table 1 you listed four medication groups. Please describe the indicator variable for medication use. Did you include one indicator for each group in the models, thus, four variables?
- It is not clear to me how the indicator variable for “individual differences in frequency of symptoms” looks like. Please add an explanation.
- You used a hierarchical modelling approach. However, you only described the first step. The description of the meta-analysis is missing.
- Sensitivity analyses: Please describe which two pollutants you used for the two-pollutant models. Were this only coarse PM and PM2.5? Furthermore, please add a sentence that you restricted your data to participants with asthma as you report results of this additional analysis. Did you perform your sensitivity analyses in both steps of your hierarchical modelling approach?
- Last paragraph: Please add the gaseous pollutants.

(1.5) Results
In general:
- Table 1, 2, and 3: Please include p-values for the difference between the cities.

Panel characteristics
- Please include information on the response rate if applicable. How many participants were for which reason excluded?
- Table 1: There are two blocks for medication use. The second one refers to
medication on demand. Does the first one refer to daily use or use at least once during the study period?

- Table 1: There are 35 total persons in Athens, however, 19 male and 15 female persons are together only 34 participants. Please clarify!

- Please add the employment status of the participants as you “made an attempt” to select non-working persons.

- Please give also information on the prevalence of cardiovascular diseases like angina pectoris or congestive heart failure. It would be interesting to check, if having a cardiovascular disease modifies the associations. For example, shortness of breath may also be a symptom of congestive heart failure.

Symptoms

- Please add the periods the participants filled out the diary per city. It is not clear if for every city the whole study period from Oct 2002 to Mar 2004 was covered. Probably, you could provide a figure with the time on the x-axis and the number of diary entries on the y-axis for each city as supplemental material.

- The number of person-days is not clear. You wrote that in total 4,764 – 5,920 person-days were available. However, table 2 provides different numbers. For example, in Athens there were 5,334+667=6,001 person-days for the analysis of associations with “woken with breathing problems” available. Furthermore, the number of person-days is partially lower than expected. Please include information on missing values in the Table 2.

- Last sentence: Is the statement of “small differences between the cities” based on a statistical test? However, I do not agree: Participants in Athens notably reported fewer symptoms and more limitations in activity than persons from the other cities.

Air pollution concentrations

- Helsinki did not have the lowest median concentrations for Ozone. That is true for Amsterdam.

- Please include information about the correlations between air pollution measures. This is important to know with respect to the sources of pollutants.

- Please make a statement about the sources of air pollution measures depending on season and city. Why are concentrations of PM2.5 and coarse particles so high in Athens whereas values for PNC were similar to the other cities? Are these differences due to different measurement periods/different sources?

- Please add the number of measurement days in Table 3.

Air pollution effects on symptoms-restriction of activities

- In the results section you only report the associations that fit to your hypotheses. However, there are several preventive effects that need to be mentioned in the text and marked in the tables:

Table 4: Shortness of breath & lag1 and lag2 of PNC; Cough and lag0 of PM2.5
and Absorbance; Table 6: Woken with breathing problems and lag2 of PM10, PM2.5 and PM10-2.5 as well as with lag06 of PM2.5; shortness of breath and lag1 of PNC. These Results also need to be discussed in the “discussion” section.

- Figure 1: I miss the results on NO2 and absorbance. In addition the OR and 95%CI for the association between PM2.5 and Wheezing in Helsinki is missing.

- Incidence analyses: In the last sentence you state that lag1 of ozone was positively associated with cough. I only see an association for lag2 of Ozone.

- For a better overview please report your results on your sensitivity analyses (two-pollutant model and restriction to patients with asthma) in an additional paragraph.

(1.6) Discussion

- Second paragraph: In a previous work from the RUPIOH study associations have been probably covered by the high prevalence of medication use. Is this also possible for your results?

- Page 13, Sentences „Nitrate and nitrite concentrations in exhaled breath condensate are a marker of oxidative stress” and “In the last two decades a substantial body…” The authors should give references for their statements.

- The differences between effects of mass metrics and PNC need to be more discussed. You found adverse effects mainly for mass concentrations. Is this probably due to the fact that a central measurement site is more appropriate for measurements of mass concentrations than for measurements of PNC? On the other side, you mentioned a very interesting point that a time series study found significant associations between PNC and cardiovascular health whereas mass concentrations were associated with respiratory health. Please elaborate on this issue.

- The results on the effects of ozone needed to be discussed. Are they in line with other studies?

- It would be easier for the reader if you mark your strength and limitations by a heading or an introducing sentence. Furthermore, please include a statement about the generalisability of your results as your study focuses on a selected population of non-working (?) patients with asthma or COPD.

(2) Minor essential revisions

(2.1) In general

The authors state that concentrations were consistently associated with most symptoms. At first sight this makes no sense to use “consistently” and “most” in parallel. It would be easier to understand if you write e.g. “…in all cities concentrations were associated with most symptoms” (Abstract, results; page 12, last sentence of the section “prevelance analyses”).

In describing RUPIOH the authors state that the study based on a more detailed
exposure assessment. More detailed than what? The second part of the comparison is missing (Abstract, background; page 5).

On page 5 in the “symptom diary” section the symptom “being awakened by breathing problems” was listed. However, later in the text and in the tables the symptom is called “woken with breathing problems”. The authors should choose one description.

(2.2) Background

Line 5: “…air quality standards or guidelines refer to PM10 and/or OM2.5.”

(2.3) Methods

Study population
- Even though you refer to another publication with more detailed descriptions it is easier for the reader to be informed about the most important aspects directly. Thus, I would suggest adding a sentence about, where the participants were recruited from.

Air pollution exposure
- I prefer to write “air temperature” instead of solely “temperature”.

QA/QC
- How did you handle deviations from the SOP?

(2.4) Results

Air pollution concentrations
- Write “air pollution measures” rather than “components”.
- Table 2, last row: write 1.0 instead of 1 (% in Athens).

Air pollution effects on symptoms-restriction of activities
- Heading: Do you mean “..effects on symptoms and limitation in activities”?

(3) Discretionary Revisions

I would prefer to replace the word “subject” with “participant”/“person”/“individual”.

(3.1) Background

- The study of Seaton et al is almost 20 years ago. I suggest adding a sentence that in meantime other studies were published (e.g. Peters, 1997, Ibald-Mulli 2004, Brook 2004, Brook 2010), and that, however, the role of ultrafine particles is still under discussion.

(3.2) Methods
Air pollution exposure
- It would be more appropriate to define your lags here rather than in the statistical analysis section.

QA/QC
- It would be nice to have the possibility to see into the SOPs. Is there a html/pdf version available on the internet?

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.