Title: Saharan dust and association between particulate matter and case-specific mortality: A case-crossover analysis in Madrid (Spain)

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Author's response to reviews: see over
Dear Editor,

Please find a 2nd revisited copy of our manuscript entitled “SAHARAN DUST AND ASSOCIATION BETWEEN PARTICULATE MATTER AND CASE-SPECIFIC MORTALITY: A CASE-CROSSOVER ANALYSIS IN MADRID (SPAIN)” to be considered for publication at the Environmental Health journal.

The manuscript has been revisited following all reviewers’ comments. We include a detailed answer to each question, also a point-by-point description of the changes made in this new version of the manuscript.

All of the authors have read and approved the revisited version of the manuscript and it has not been published previously nor is it being considered by any other peer-reviewed journal.

Yours sincerely,

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ANSWERS TO REVIEWER MARC SAEZ

Minor Essential Revisions:

Data section. Why the authors consider also 'cerebrovascular mortality'? Evidence in the literature is not very clear. Please, discuss a little why these and not other causes were analyzed.

The reviewer is right. Evidence of literature is not very clear about short-term effects of particulate matter on cerebrovascular mortality. However, a recent study conducted in another Spanish city, Barcelona, with a similar setting like ours, reported an association between particulate matter and cerebrovascular mortality (Pérez et al. Environ Sci Technol 2009). However, they did not assess for the role of Saharan dust intrusions. Thus, we decided to include this case specific type jointly with the usual case specific types, such as cardiovascular and respiratory mortality.

Data section. Why authors do not try to do a stratified analysis by age group? Or, at least, considering younger and older than 65 years old? Please discuss this point.

Although from a pathophysiological point of view there it is well known that the elderly group is most vulnerable to the short-term effects of air pollution on health, we have not considered conducting analyses by age group due to, unfortunately, these data was not available. We have addressed this issue as a limitation in the Discussion section (please see below answer to next question).

Discussion section. Please discuss the potential effect of other confounders such as contextual socioeconomic status (i.e. 'areal' socioeconomic status) and other potential effect modifiers such as age, sex, etc.

The reviewer is right, as a potential limitation, we have not addressed for contextual socioeconomic status and other potential modifiers, such as age and sex. However, the study design that would have meant a spatial adjustment had been very different to that conducted in our study. From a pathophysiological point of view there it is well known that the elderly group is most vulnerable to the short-term effects of air pollution on health, we have not considered age groups due to these was not available. As reviewer suggests, we have now addressed this issue as a limitation in the Discussion section (please see second paragraph, Page 10):

“As limitation, we have not addressed for contextual socioeconomic status and other potential modifiers, such as age and sex. However, the study design that would have meant a spatial adjustment had been very different to that conducted in our study [24]. From a pathophysiological point of view there it is well known that the elderly group is most vulnerable to the short-term effects of air pollution on health [25], we have not considered age groups due to it was not available.”
Could you please redraw Figure 1 with the four causes in the same Figure?

As the reviewer suggests we tried to draw Figure 1 with the four causes in the same figure. Unfortunately, this redraw showed a misleading figure due to it displayed 40 estimates (five lags by Saharan and non-Saharan days by four causes of mortality!). For this reason, we decided to split it into four figures, on for each case specific type of mortality. However, the reviewer should note that both axes for each figure are displayed in same scale to be fully comparable.
ANSWERS TO REVIEWER LUCA MATASSONI

Major compulsory revisions.

The authors with others published a short note closely related to this manuscript, results are not compared or even cited in the references, probably due to its recent publication. The paper under review show a case-specific and seasonality analysis absent in the previous note, but it concerns essentially the same database (although with three additional codes) analysed by the same methodology. No mention for the other available data in addition to PM10 values, such as the concentration values of PM2.5, SO2, NO2 and O3. Therefore, it must be clarified whether any change in these parameters associated with Saharan dust has been evaluated in the statistical analysis or not.

The reviewer is right. We firstly conducted a previous analysis (recently published in: Tobías et al. Stoten 2011) following to replicate a study conducted in another Spanish city, Barcelona, with a similar setting like ours. Unfortunately, it review process took too long and meantime other three papers on the same topic were published, in Italy (Sajani et al. Occup Environ Med 2011) and Greece (Samoli et al. Environ Res 2011).

As the reviewer has noticed, although we did not mention we also considered concentrations of gaseous pollutants (NO2, SO2) and ozone. Concentrations of these did not differ from Saharan and non-Saharan days. Also, all PM10 reported estimates have been adjusted for gaseous pollutants and ozone. We have now clarified this point: i) updating Methods section (please see Data sub-section, Page 5); ii) reporting levels of these pollutants in Table 1 (please see Page 17) also in the first paragraph of the Results section (please see Page 7); iii) noticing in the Methods section that all estimates are also adjusted for a 4 day-average linear terms of gaseous pollutants and ozone (please see Statistical analysis sub-section, Page 6); iv) Finally we have cited our recently published work as new reference num. 20

About the only use of PM10, in our recently published work we did not found differences between Saharan and non-Saharan dust days for PM2.5. Also, for the study period (2003 to 2005) PM10 levels were the only measurement of particulate matter required for air quality guidelines. In addition, the recent studies published in Italy and Greece mainly focused on the health effects of PM10. For these and as the reviewer pointed out that our manuscript covers a topic of considerable importance in the ongoing debate on the mortality induced by the influx of Saharan dust in southern Europe, is therefore a need for studies to be fully comparable in terms of the causes of mortality and air pollutants evaluated. Due to the importance of this point, we have address it in the Discussion section, including the following new paragraph in Page 9:

"However, we did not consider other PM fractions since from a previous study we did not found differences between Saharan and non-Saharan dust days for PM2.5 [20], and no PM1 levels were monitored during the study period. Nevertheless, the
issue of harmful effects of Saharan dust has recently been addressed by taking PM10 into account, as recently did in the Emilia-Romagna region [11] and in Athens [12]. Thus, our study is entirely comparable with those in terms of outcome and exposure evaluated, increasing the ongoing evidence on the mortality induced by the influx of Saharan dust in southern Europe.”

Minor essential revisions

Background (page 1, paragraph 1): change from ‘... the areas closest to the great deserts are those...’ to ‘the areas which are closer to the great deserts are the...’

As reviewer suggests, we have now modified this sentence in the Background section.

Data (page 4, paragraph 1): the web link to the data must be better identified and more detailed with the date of the last access. Methodology used for identification of the Saharan dust days must be indicate;

As reviewer suggests, we have now better indicated and detailed the web link and described the methodology used for identification of Saharan dust days in the Methods section (please see Data sub-section, Page 5).

Results (page 5-6): change from 'Overall, mortality due to circulatory causes represent 30% of total mortality due to organic causes,...' to 'Overall, organic causes represent 48% of the total mortality, circulatory causes 30%, respiratory causes 15% and cerebrovascular causes 7% (Table 1).'

As reviewer suggests, we have now modified this sentence in the Results section.

Results (page 6, paragraph 2): change ‘largely’ with 'larger’ and delete' (organic: 1.70% ... (95% CI:0.6, 2,27))’ inserting the data into table 2 by a new row named 'whole year' (see below);

As reviewer suggests, we have now modified this sentence in the Results section, also inserted whole year risk estimates in Table 2.

Results (page 6, paragraph 2): change 'not statistically significant' to 'not statistically significant (Table 2)' and from 'Table 2 shows findings when stratifying by..' to 'Table 2 shows results also stratified by ...'

As reviewer suggests, we have now modified both sentences in the Results section.
Results (page 6, paragraph 3): to improve readability replace the brackets delimiting the confidence interval with square brackets, e.g. from ‘(95% CI: 1.01, 4.08))’ to ‘[95% CI: 1.01-4.08])’; change from ‘... during warm season risk was larger for Saharan non-dust days’ to ‘... during warm season risk was larger for Saharan dust days’;

As reviewer suggests, we have now replaced brackets to delimit confidence intervals. We have also modified the sentence in the Results section.

Discussion (page 8, paragraph 3): change from ‘... travelling from the Sahara to Southern Europe [11,22].’ to ‘... travelling from the Sahara to Southern Europe [4,11].’ because paper cited as [22] was above already cited as [4].

As reviewer indicates, we have now updated and re-numbered all references in the manuscript.

Reference: references must be written following the formatting guidelines of the journal; delete duplicated reference [22] and correct the numeration of subsequent references (also in the text).

As reviewer indicates, we have re-numbered all references also updated following journal’s guidelines.

Table 2: insert an ‘whole year’ row with related data (see above); clarify the title changing to ‘Association at lag 1 between an increase of 10 microg/m3 of PM10 and daily case-specific mortality during Saharan dust and non-dust days, also by season*’

As reviewer suggests, we have now updated Table 2 inserting a whole year row with related data.

Discretionary revisions

Discussion (page 7, paragraph 1): change from ‘For respiratory causes these effects were larger during Saharan dust-days in the cold season, while for circulatory causes were larger in the warm season.’ to ‘Therefore, during Saharan dust-days these effects were larger in the cold season for respiratory causes and in the warm season for circulatory ones.’

As reviewer suggests, we have now modified this sentence in the Discussion section.

Discussion (page 7, paragraph 2): change from ‘... and, intriguingly, on the contrary to the...’ to ‘... and, on the contrary, different from that...’
As reviewer suggests, we have now modified this sentence in the Discussion section.

**Conclusion:** change from 'We also observed evidence of strongest effects of PM10 on respiratory mortality during Saharan dust intrusion in the cold season and due to circulatory causes in the warm season...' to 'During Saharan dust intrusion we also observed effects of PM10 on mortality due to respiratory causes in the cold season and to circulatory causes in the warm one.'

As reviewer suggests, we have now modified this paragraph in the Conclusions section.

**Figure 1:** change the caption to 'Percentage increases of case-specific mortality for an increase of 10 microg/m3 of PM10, from lag 0 to lag 4, during Saharan dust (with circle) and non-dust days (back squares) with 95% confidence interval (vertical lines).'

As reviewer suggests, we have now modified the caption for Figure 1.

**Table 1:** change from 'case-specific mortality' to 'daily case-specific mortality' and from 'particulate matter' to 'PM10' in the title.

As reviewer suggests, we have now modified the title for Table 1.

The results of the study may be compared with some papers related to very similar issues although are not focused on Saharan dust outbreaks and PM10

Although we did prefer to focus the Discussion of our manuscript under the main objective to evaluate the role Saharan dust intrusions on the association between particulate matter and daily case-specific mortality, we agree with the reviewer and we have compared our results with others also related to case specific mortality and PM10 but not focused on Saharan dust outbreaks. Thus, we have now included a brief statement on the Discussion section (please see beginning of third paragraph, Page 8):

“The overall effects of PM10 on case specific mortality found in our study agreed with those previously reported in other European cities. The APHEA-2 study reported that an increase in PM10 by 10μg/m3 was associated with increases of 0.76% in cardiovascular deaths and 0.58% in respiratory deaths [17].”