Author’s response to reviews

Title: Desert dust outbreaks and respiratory morbidity in Athens, Greece.

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Author’s response to reviews:

RESPONSE TO THE EDITORS AND THE REVIEWERS

We thank the Editors and the Reviewers for the careful review of our manuscript and their insightful comments. Following these suggestions, we have performed a substantial revision of the manuscript. Please find in the following the responses to the specific comments. We have highlighted all additions or modifications with yellow.

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Response to the Editors’ comments

Editors’ comment: “While both reviewers see merit in your paper, they both identify important issues that will require additional analysis. Carefully reconsider your definition of a desert dust day.”

Response:

Thank you for the opportunity to revise our paper. We have now greatly revised the paper according to the Reviewers’ suggestions, when this was possible due to data availability. Regarding the definition of desert dust days: As we describe in the responses to the Reviewers’ comments and particularly to the first Comment of Reviewer 1, we have applied an additional definition for identification of desert dust and non-desert-dust days following the criteria used in the MED-PARTICLES project (reference #22). The identification of the days was provided by J. Pey whose contribution we now acknowledge in the paper. We proceeded with analysis...
restricted to these days and our results remained robust. This has been described in detail in the Methods (Lines: 101-105) and in the Results sections (Lines 156-160) as well as in the Supplementary Table S2 of the revised manuscript.

Response to Reviewer #1:

Reviewer’s comment:

“The authors investigate the association between desert dust outbreaks and respiratory morbidity in Athens, Greece. Furthermore, they try to address the (possibly) independent effect of PM10 concentrations, also adjusting for co-pollutants. Compared with previous publications, the authors limit the analyses to a small sample of days during their study period: 132 with dust advections, and 177 matched days with no advections, and similar distributions in terms of days of the week-month-year, temperature and humidity.

In general, the paper is interesting in its field, because it addresses a topic with conflicting evidence, and it does so focusing on an outcome, respiratory morbidity, with clear a priori biological plausibility. However, there are several methodological choices which require further clarification.”

Response:

We thank the Reviewer for his comments and input.

Reviewer’s comment:

“1. Identification of desert dust days. The authors applied a combination of back-trajectories and high PM levels in rural stations, and they identified 10% of the days during the study period, 2001-2006, as dust affected. I would strongly suggest the authors to use, as sensitivity analyses, other approaches, such as atmospheric models for example, and see whether additional days are identified. Furthermore, there are several approaches suggested in literature to quantify the dust burden attributable to desert episodes. These might be applied to better select cases and controls.”

Response:

We thank the Reviewer for this critical remark and following his suggestions we performed sensitivity analyses using other approaches. Specifically, for the period of our analyses we defined a day as “a desert dust” or not following the criteria used in the MED-PARTICLES project (reference #22). The identification of the days was provided by J. Pey whose contribution we now acknowledge in the paper. Comparison of the characterization by the two methods
resulted in 81 dust days and 110 control (non-dust) days denoted as such by both approaches. We proceeded with analysis restricted to these days and the results remained robust. Unfortunately due to availability of morbidity data only in the initially pre-specified days it was not possible to expand the analysis to all the days identified under the Stafoggia et al. approach. A paragraph has been added in the Methods (Lines: 101-105) and in the Results sections (Lines 156-160). Also, we added Supplementary Table S2.

Reviewer’s comment:

“2. Case-control approach. It is not clear how the case-control matching is retained in the analysis, and how the authors solve the problem of discontinuous time series introduced by the selection of the studied days. In other words, by including only 300 days in the analysis, all the advantages of time series approaches are lost, and it is not clear how the use of dummy variables for year: month can solve this problem.

Furthermore, while it makes sense to match control days to case days by some parameters (DOW, month, temperature), it is not clear how such matching is accounted for in the following Poisson model. I would suggest the authors to apply, as sensitivity approach, an alternative model where the whole time series is used. In this way the estimate for PM10 would be more robust and reliable, whereas the estimate now provided is not, because it only refers to 300 days and it is not clear how it is driven by other time-varying factors such as season and meteorology (for example more dust days occurring on specific seasons, and the same for control days since they are matched by month and temperature).”

Response:

Unfortunately we do not have morbidity data for the whole period of the analysis as now extensively clarified below (please see our response to comment 3). As the Reviewer correctly notes, the analysis cannot fully incorporate the advantages of a standard time series but nevertheless this is the kind of modeling dictated by the structure of the data, as morbidity counts per day, our dependent variable, follow a Poisson distribution. We have opted for control for time factors using indicator variables a method often applied in epidemiological analysis of short-term effects, as for example in case-crossover analysis. Finally the pattern of the matching which is on exposure and not on disease does not allow to fit a conditional logistic model.

Reviewer’s comment:

“3. Study period. It is 2001-2006. Authors should do their best to expand to a more recent period. Since the study is single-city, it is not so novel and powerful. Authors should try to expand the
series and do additional analyses to provide new result in a study not entirely original from the start.”

Response:

We thank the Reviewer for this suggestion. Unfortunately in Greece there are no electronic records for emergency room visits and relevant data, such as demographics, diagnostics, performed examinations and outcome (i.e. discharge or admission, recommendations to the patient etc). All data analyzed for the present work were therefore collected manually by reviewing the emergency department books kept in the hospitals’ archives only for the a-priori defined desert dusts days and their matched control days during the study period. We now explain this procedure better in the methods (lines 88-92) and mention it in the study limitations in the Discussion (lines 254-257).

Reviewer’s comment:

“4. Role of dust in the PM-morbidity relationship. It is not clear, from the study hypothesis, whether dust occurrence is considered as a confounder or an effect modifier in the PM-morbidity association. This is quite crucial for the interpretation of the results. I would suggest the authors to provide a DAG and to explain the meaning of the arrows pointing to resp. morbidity in terms of independent vs confounded or mediated effects of dust and PM.”

Response:

We thank the Reviewer for the opportunity to try to disentangle the effects. We have now clarified our rationale in the discussion, lines 216-226 of the revised manuscript where we write: “The effects of dust could be attributed to a complex mixture of factors, including the change in the concentration and profile of particles, the lowering of the layer boundary height or/and the transport of pollen or bacteria. We hypothesized that although the greater part of desert dust effects may be attributed to particles’ effects there may also be other mechanisms, as for example the lowering of the boundary height may create a more toxic air pollution profile multiplying the effects of various air pollutants. Unfortunately we have no data to test any of these hypotheses. Hence, we consider the dust as an effect modifier for PM mass health effects, and PM separated in two components: one as a mediator of dust effects and another mainly characterized by PM from local emissions acting as an independent risk factor. However we only have one measurement for the total mass of PM and we can only approach the 2 components by testing the interaction of PM with desert dust days. The proposed associations are schematically depicted in Figure 1.” We have also added a figure, Figure 1 of the revised manuscript, with a proposed DAG for this association.
Reviewer’s comment:

“5. Distribution of other pollutants. Finally, the authors should explain in more details why the other pollutants are higher on non-dust days. Is it because anthropogenic emissions are lower on dust days, or because dust episodes tend to occur on periods with lower pollution in general? This might explain why PM is only moderately higher on dust days compared with non-dust days.”

Response:

We thank the Reviewer for giving us the opportunity to expand on this issue. Indeed, the dust episodes tend to occur in spring (31.1% of dust days) or fall (28% of dust days) that are periods with lower pollution in general. This is reflected in the non-desert-dust days as these are matched for month and weekday. A paragraph has been added in the results section (Lines 111-116). Moreover, we have also included a Table (Table 2) showing the distribution of days with desert dust events by season and year.

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Response to Reviewer #2:

Reviewer’s comment:

“The authors present results of a time-series study assessing associations of desert dust days, PM10, and respiratory emergency department (ED) visits and hospital admissions during 2001-2006 in Athens, Greece. Transported desert dust can alter local PM size distribution and composition, including potentially health-relevant biogenic content. This manuscript thus tackles an important topic and adds to the literature on transported desert dust and health in Europe.

Overall, the manuscript could be strengthened by inclusion of additional details and interpretation, as well as results of sensitivity analyses to support observed associations.”

Response:

We thank the Reviewer for her comments and input.

Reviewer’s comment:

“MAJOR COMMENTS

1. Focus of analyses considering desert dust effects. The authors suggest that desert dust may contribute to increased respiratory morbidity through increased PM10 levels as well as by altering PM size and composition. While the authors consider modification of dust effects by PM10, the majority of the manuscript is focused on desert dust effects adjusted by PM10
(and vice versa). The authors should discuss and interpret this focus more throughout - i.e., PM10 is not a traditional confounder in this context; and, by controlling for PM10 in the analysis, one can perhaps tease apart the non-mass related effects dust days. While the authors touch on this in the discussion, justification and interpretation of the different forms of analyses (adjustment vs. effect modification) could be clarified throughout.”

Response:

We thank the Reviewer for giving us the opportunity to try to disentangle the effects. This point has been also raised by Reviewer 1. We have now clarified our rationale in the discussion, lines 216-224 of the revised manuscript where we write: “The effects of dust could be attributed to a complex mixture of factors, including the change in the concentration and profile of particles, the lowering of the layer boundary height or/and the transport of pollen or bacteria. We hypothesized that although the greater part of desert dust effects may be attributed to particles’ effects there may also be other mechanisms, as for example the lowering of the boundary height may create a more toxic air pollution profile multiplying the effects of various air pollutants. Unfortunately we have no data to test any of these hypotheses. Hence, we consider the dust as an effect modifier for PM mass health effects, and PM separated in two components: one as a mediator of dust effects and another mainly characterized by PM from local emissions as an independent risk factor. However we only have one measurement for the total mass of PM and we can only approach the 2 components by testing the interaction of PM with desert dust days. The proposed associations are schematically depicted in Figure 1.” We have also added a figure, Figure 1 of the revised manuscript, with a proposed DAG for this association.

Reviewer’s comment:

“2. Identification of desert dust days. Ultimately, the authors find little difference in PM10 levels between dust and non-dust days (Table 1), and they do not find any modification of desert dust effects by PM10 (lines 123-124). Some additional discussion on how desert dust days were identified is warranted. The authors classify days as a 'desert dust day' if: a) air mass transport occurred from the Sahara or the Arabian Peninsula (using back-trajectory analysis); and, b) if the ratio of PM10 from a remote to a centrally-located monitor was high (greater than the median for the year). Can the authors clarify the second criterion?

By remote vs. centrally-located monitors, do the authors mean rural (outside of Athens) vs. urban (inside the study area)? And, if so, on days with high desert dust, would these impacts be regional and thus impact both monitors similarly and/or simultaneously? Why not specify the criterion as high PM10 levels at the central site (relative to the season)?”

Response:
We thank the Reviewer for giving us the opportunity to clarify this issue. We have now expanded clarified in the Methods, lines 63-64 that this referred to “…the ratio of the PM10 concentration measured at a suburban monitor located at the outskirts of the Athens north region to an urban monitor in the center of the town…”. Following also our response to the first comment of Reviewer 1, we have now also used for the identification of dust days a method applied previously in the MEDPARTICLES project and applied this in a sensitivity analysis that revealed robust estimates. This is described now in the Methods, lines 101-105 and the respective results are described in the Results, lines 156-160 and shown in Supplemental Table 2.

Reviewer’s comment:

“3. Descriptive comparison of dust and non-dust days. The authors provide some characterization of desert dust days in Table 1, in which comparisons with non-dust days on various factors are made. Some additional characterization regarding the temporality and occurrence of desert dust days throughout the 6-year dataset is warranted. For example, when do dust days tend to occur (e.g., in certain seasons and/or years)?”

Response:

Following this suggestion, we added Table 2 in the revised manuscript showing the distribution of desert dust days by season and year. The following paragraph has been added in the Results section (Lines 111-116). “The distribution of days with desert dust events by season and year, presented in Table 2, reveals that dust episodes tend to occur on spring (31.1% of dust days) or fall (28% of dust days) that is periods with lower pollution in general. Matching was on a number of factors associated with the levels of pollution restricted the range of pollutants observed. Over the 6 years of the examined period, there were differences in the yearly distribution with highest occurrence of events in 2001, 2002 and 2004 and considerably less dust events in the other years.”

Reviewer’s comment:

“4. Magnitude of effect estimates for desert dust days. The authors consistently observe very strong associations of desert dust days and respiratory morbidity (with estimates of ~50% increase risk of ED visits or admissions on dust days compared to other days). This magnitude of association is much larger than in other air pollution time-series studies, in which % increases in risk of 1-5% are usual (as observed for PM10 in this study). How do these results compare to previous studies of desert dust and health? Could uncontrolled confounding explain these very strong associations? To negate such concerns, the authors might present results of sensitivity analyses with tighter control for time (see minor comment 6 below), and consideration of other
episodic environmental factors (e.g., pollen levels?) that could plausibly confound the observed desert dust effects.”

Response:

We agree and thank the Reviewer for raising this point. Indeed, as the reviewer points out, the estimates for the biological effects of dust events were in a magnitude that is much higher than that reported from air-pollution studies. Nevertheless, Samoli et al (2011) also reported a high dust effect of 2.97% increase in total mortality vs 0.71% increase associated with PM10 increase of 10 μg/m3. Comparison with other studies is not feasible due to different approaches to investigate the association (for example fine and coarse concentrations, mass contributions in PM10 due to desert dust) and absence of reporting on the dust indicator effect. Considering that in epidemiological studies effects associated with dummy variables or from small studies (as the present one) report higher estimates, we believe that our estimates are possibly over-estimating the true effects. Unfortunately, lack of data for pollen or particles’ components data in the Athens’ region for the study period does not allow us to perform further sensitivity analyses. We have now added these restrictions to our discussion (lines 226-228).

Reviewer’s comment:

“MINOR COMMENTS

1. Lines 33-34 - the authors indicate that desert dust outbreaks alter particle size distribution and composition. Some additional discussion is warranted in the introduction on how/why PM size and composition is altered during dust outbreaks, and clarification on what the comparison is (i.e., altered compared to 'general' urban PM in Europe)?”

Response:

Following the reviewer’s suggestion, we have addressed this issue in the background (Lines 33-40) of the revised manuscript by adding the following paragraph: “Recent evidence has shown that desert dust outbreaks alter particle size distribution as well as their chemical composition [9-12]. This effect depends on several factors such as the dust origin as well as the transportation route until the dust reaches the particular destination. Previous studies have indicated an increase in crustal elements of PM2.5 in dust days compared with non-dust days as well as differences in the concentrations of selected metals of larger particles [13]. Additionally, there is evidence for a microbial component of the transported dust [14]. However, from the limited number of studies carried out to establish the health effects due to the desert dust source, there are conflicting results [15].”
Reviewer’s comment:

“2. Lines 61-64 - the authors selected ‘control days’ (or non-dust days) for descriptive comparison with the identified desert dust days. Control days were selected as the same day of week, same season, and similar temperature and humidity as the dust day. Please clarify how was season specified here - i.e., within the same season and calendar year? If not within the same calendar year, then perhaps some of the differences (or lack thereof) in comparison between day types could be due to long-term temporal trends.”

Response:

The following sentence was added in the Methods section (Lines 68-70) to clarify this issue: “Same season was defined as the same season within the same calendar year with exception of the winter which extended from December of a given year to February of the next year.”

Reviewer’s comment:

“3. Lines 65-66 - please specify the temporal metrics of daily air pollution concentrations of interest; were these all daily 24-hr average data used in the epidemiologic models?”

Response:

The following clarification has been added in the Methods section (Lines 72-73): “…for PM10 and NO2 daily 24h average data, for O3 daily 8h maximum data.”

Reviewer’s comment:

“4. Lines 67-69 - how many hospitals provided data towards the study, and approximately what fraction of respiratory ED visits and hospital admissions among the Athens population were captured?”

Response:

During the reported time period, 19 Pneumology departments were participating in the emergency services network of the Athens region. The data presented were collected in 16 of these 19 Pneumology Departments. In the three remaining departments, respective data could not be collected due to loss or destruction of the emergency department books after a natural disaster (flood). Although we cannot provide an exact percentage, the presented data represent the overwhelming majority of respiratory emergency department visits and admissions in the Athens region. This has been clarified in the Methods, lines 76-77, where we write: “…in 16 out of 19
pulmonary departments (84%) participating in the emergency services network of the Athens’ Metropolitan Area”.

Reviewer’s comment:

“5. Lines 80-81 - please specify the lag structure used to assess associations between dust days, pollution, and respiratory morbidity. How was lag structure determined?”

Response:

We have now clarified in the text, lines 95-96, that “For both PM10 and for dust events we used lag 0 as an a-priori choice.”

Reviewer’s comment:

“6. Lines 80-81 - the authors controlled for long-term time trends and seasonality using a two-way interaction between year and month. Given within month trends in respiratory morbidity during some times of the year, I wonder whether smooth control for time may be needed in this analysis.”

Response:

Unfortunately as we do not have morbidity data for the whole period of the analysis and our observation days are scattered within the period 2001-06, the analysis cannot fully incorporate the advantages of a standard time series. Exactly due to the discontinuing time trend we have opted for control by dummy variables instead of a continuous function such as splines that is usually applied in epidemiological time series analysis.

Reviewer’s comment:

“7. Lines 80-81 - if I have interpreted the text correctly, it appears that all 6-years of data were included in the main Poisson models (not only the selected dust and non-dust days characterized in Table 1). If so, the authors should clarify that the dust effects are in comparison to all other days in the time series (i.e., methods, results text, and tables).”

Response:

We thank the Reviewer for the opportunity to clarify this issue. Actually, data were collected only for the days that were identified as days with desert dust events as well as for the selected
control days. We have now clearly stated this in the Methods section (lines 75-76 and lines 90-92) of the revised manuscript.

Reviewer’s comment:

“8. Lines 89-91 - Table 1 shows the descriptive comparison of desert dust vs. non-dust days. Since these days combined make up only a small subset of the full 6-year dataset used in the Poisson models, I suggest including in Table 1, or as a separate table, descriptives of the full time period.”

Response:

Following the Reviewer’s suggestion, we have added a column in Table 1 showing the descriptives of pollution and meteorological data for the whole 6-year period. Health data were available only for a small subset of days within 2001-06, namely for the days identified as desert dust days and for their controls.

Reviewer’s response:

“9. Lines 94-96 - patient age was missing for 14% of visits. What is the basis for replacing these missing values with the mean age of patients with the same diagnosis? I imagine that doing so adds noise to stratified analyses assessing effect modification by age. I suggest reporting results for age stratified analyses excluding those visits with missing age information.

Response:

We have now applied the sensitivity analysis suggested and updated the text in the Methods (lines 100-101) and Results section (lines 161-166). Specifically we have added that “Results from the sensitivity analysis in the subgroup of patients with complete information on their age provided similar results both in the magnitude of the effects and in the statistical significance. For example, the percent change in emergency room visits for respiratory causes in the mutually adjusted model for those <65 years was 0.53% (95% CI: -1.48%, 2.58%) per 10μg/m³ increase in PM10 and 53.20% (95% CI: 32.56%, 77.06%) for the dust indicator; for those >65 years the corresponding estimates were 0.51% (95% CI: -1.67%, 2.74%) and 46.19% (95% CI: 24.88%, 71.14%).”
“10. Lines 155-156 - please provide further discussion of the advantage of focusing on respiratory morbidity; what do the authors mean by 'plausible biological explanation'?”

Response:

We thank the reviewer for giving us the opportunity to clarify this issue. The following paragraph has been added in the Discussion section (lines: 194-202) of the revised manuscript:

“The respiratory system belongs to the systems of the human body, for which there is convincing evidence for a significant influence exerted by meteorological and atmospheric conditions and an associated effect on morbidity [29-31]. Thus, it seems plausible that adverse effects of an increased pollution burden and of altered atmospheric conditions due to desert dust outbreaks would manifest predominantly in the respiratory system. Indeed, several mechanisms for an adverse effect of particulate matter on the respiratory system have been proposed including for instance local inflammatory reaction [32], the induction of a systemic inflammatory response augmenting lung inflammation [33], or cytotoxicity and oxidative damage [34,35].”

Reviewer’s response:

“11. Table 4 - please clarify the results layout. Are all results adjusted for the stated pollutant (NO2 or O3) and then PM10 and dust are added individually and combined, in addition to the gases already in the model? Inclusion of the single-pollutant associations for NO2 and O3 would provide a more complete picture of the results.”

Response:

Our main analysis model does not include gases. Following the reviewer’s suggestion, we have now added Supplemental Table S1 to present the effects of gases on respiratory morbidity but as these are not directly connected to our research hypotheses, we have restrained from including them in the main text.