Author's response to reviews

Title: A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: The effect of short-term changes in air pollution and dust storms.

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Author's response to reviews: see over
The Editor, Environmental Health

Dear Editor,

Re: A 10-year time series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effects of short-term changes in air pollution and dust storms.

We are pleased to accept your offer to resubmit a revised version of the above paper. The paper investigates two related issues: (a) the effect of short-term changes in levels of particulate matter (PM) and ozone on the risk of hospitalization in the capital of Cyprus, Nicosia and (b) the separate possible health effects of PM from dust-storms, frequent in this region. It was rewarding to see that the reviewers have recognized the original contribution made by the paper in both respects. While there has now been some overwhelming evidence on adverse health effects of daily changes in levels of air pollution, this commonly comes from large studies that combine estimates from several cities, commonly capital or large-size cities. Associations are not often investigated in smaller-size cities, such as Nicosia where PM$_{10}$ concentrations are comparable with the high levels seen in much larger Southern European cities such as Athens, Tel Aviv and Milan. The long period of investigation (i.e. 10 years, much longer than in similar time-series studies) has allowed inferences to be drawn from a relatively small-size city. The pattern and magnitude of effects observed here, as the reviewers also point out, appear consistent with the effects observed elsewhere.

Of course, of particular interest, and an integral part of this paper, is the second issue investigated here i.e. long-range transport of dust into Southern Europe from desert regions raising PM concentrations several times above international recommendations. There haven’t been many studies that have considered this issue internationally, even less so in Europe. In fact, there is some conflicting evidence in the literature as to whether PM from natural phenomena poses the same risk on health and, thus, findings from this study will be of interest to an international audience. With dust-storms common in the Mediterranean and Southern Europe, Nicosia offers a natural setting to investigate this issue and thus add to the current evidence, as indeed the reviewers acknowledge. We have now addressed all of the important issues and recommendations raised by the reviewers and made some additional small editing changes. All authors have seen and approved the revised draft. We look forward to receiving your response.

In more detail, we have addressed the reviewers’ suggestions as follows:
Referee 1: Ferran Ballester

Intro: As was the case with the other two reviewers, the reviewer acknowledges both the contribution of the paper as well as the appropriateness of Nicosia, where dust storms are frequent, as a natural setting in investigating this new and relevant matter.

Point 1: We have now clarified that the three data-based criteria were not used to identify dust-storm days per se. The basis of the calendar of dust-storm events was predominantly constructed based on meteorological observations i.e. by reviewing paper-form records from the main Airport in Cyprus to identify days when a meteorological observer (as part of their hour-by-hour coding of weather and visibility conditions) noted “dust in suspension”, that did not refer to either “haze” or “dust from local sources” i.e. a result of re-suspension. The criteria were subsequently (and only) used to confirm, invalidate or propose additional days with the aim of categorising days into confirmed events, where all the criteria suggest an event that might have been overlooked or coded otherwise by the afterall subjective judgment of the observer. As a last step, identified events were also cross-checked using backwards trajectory models ending in Cyprus on the time the meteorological observation was made to track and confirm their source in the Sahara or the Arabian peninsula – see revised description in Identification of dust-storm days, Methods. Thus, as explained in the Limitations, Discussion while it is likely that some dust storms, especially those of milder intensity, might have been missed out, it is unlikely that days with high levels of PM solely due to traffic sources were considered as dust-storm days.

Point 2: The ICD code refers to the diagnosis of each inpatient admission. As it is true with all hospital data, there might be misclassification of the cause of admission, particularly in people with joint respiratory and cardiovascular pathologies. However, it is unlikely that such misclassification is temporally related to levels of air pollutants and, thus, can only bias our estimates towards the null – this point was explained in the Limitations, Discussion.

Point 3: The main analyses, as well as all of the results presented in the tables, refer to exposure as recorded in Nicosia Central station for which air pollutant measurements were available for most days in the 10-year period. With missing values only in about 10% of all days (and an additional 2-3% days purposefully excluded due to availability of less than 12 hourly measurements), the completeness of the main series used for analysis concurs with previous practice, including the protocol used in APHEA, since stations are commonly excluded if more than 25% of the values are missing. The background station was mainly used to aid in the identification of dust-storm days and for sensitivity analyses. Data from this station were available for 6-8 years, a period of investigation still longer than used in similar time-series studies. Similarly, in this period only about 10-15% of days were missing. Imputation of the missing values was not considered. Commonly, previous studies have replaced missing values using a weighted average of other monitor stations at that day. In our case, this that was not necessarily feasible for two reasons: (i) there was only 1 other station, at a rural location and (ii) as availability of data from that station did not cover the full period of investigation, it would only replace
20% of all missing values. We have now explained these issues in para 1, Data and data sources, Methods as well as in the Limitations, Discussion.

**Point 4:** Sensitivity analyses were indeed carried out for the reduced time-period for which the background station was running. This rural station does not necessarily describe the exposure experience of the population in Nicosia, yet it generally showed some similar associations and patterns. For example, a comparable 0.81% 95%CI (0.36, 1.27) increase in all-cause admissions was estimated per 10µg/m³ increase in same-day levels of PM₁₀ as recorded in the background station. Furthermore, while generally statistically non-significant, a similar pattern of effects at lagged exposure with levels of ozone was observed at the rural station. We have now commented on that fact in the text were relevant, for example para 3, Results and para 3, The effect of short-term changes in air pollutants on hospitalization, Discussion.

**Point 5:** In each case, model fit was assessed by inspection of the overdispersion parameter, the model deviance as well as the pattern and magnitude of residual autocorrelation. We have now clarified that starting with 40 degrees of freedom (a practical and meaningful choice to represent 4 seasons over the 10 year period), the degree of smoothing for seasonality was assessed by inspecting the pattern and minimizing the absolute sum of the partial autocorrelation function. Consistent with previous practice to describe long-term seasonality without risking oversmoothing and, thus, eliminating patterns due to the exposure under study, windows below 2 months were generally not considered. All models were checked for remaining autocorrelation by examining plots of the partial autocorrelation function. Autoregressive Poisson models were considered were necessary and inferences were generally unaffected. We have now clarified these issues on the use of diagnostic tools in Statistical analyses, Methods.

**Point 6:** We agree with the reviewer that it would be interesting to explore lagged exposure beyond the two previous days, particularly in the case of ozone which unlike PM showed lagged associations. However, as the second reviewer accurately points out (para 1), multiple testing across sub-groups and at different lags can produce spurious associations simply due to chance. To avoid these problems, it was decided *a priori* that only lagged exposure for up to two previous days would be investigated. Ideally distributed lag models should be used in this case; however, these were not suitable here due to the limited statistical power with small number of daily admissions in a city the size of Nicosia.

**Point 7:** We agree with the reviewer that the effect estimate during the warm months was short of statistical significance, at least at the 5% level. However, we should note that of equal importance in this case is the pronounced difference between the estimates during cold and warm months and, hence, evidence of a differential effect by season. We rephrased the description in the text to more accurately reflect the results and convey the uncertainty around our conclusions – see Results, para 5.

**Point 8:** We have now revisited and expanded the Limitations section in the Discussion to more explicitly acknowledge the points the reviewer suggested, namely, the definition of dust-storm days, missing data, misclassification of outcome, small sample size.
**Reviewer 2: Alain Le Tertre**

**Para 1:** As the reviewer accurately points out the paper deals with the original issue of health effects of particulate matter from dust-storms, an issue that, to quote the reviewer “…only a few papers are trying to quantify…”. His concern about the possibly large number of models (across sub-groups and at different lags) is justified as it is true that multiple testing might produce some spurious associations. However, we fully agree with him that the observed consistency of patterns and estimates (both internally as well as with studies elsewhere) gives credibility to the main findings. This is precisely why we *a priori* restricted the analysis to (a) gender-specific or age-specific associations only as well as (b) for lagged exposure of up to the two previous days. While we had already acknowledged this issue in the paper (Results, para 4), we have decided to also comment on it in the Limitations, Discussions. Models investigating effect modification and non-linearity across quartiles are only complimentary to the main analyses, nevertheless necessary in the first case to highlight important differences by season and, in the case of the later, to provide a basis of comparison (and a similar unit of measurement) between dust-storm and non-storm days.

**Para 2:** We have now clarified both that (a) outlier in the case of the third criterion used in identifying dust-storm events was defined as 2 SDs away from the predicted value based on meteorological conditions and levels the previous day and (b) estimates across quartiles, as well as the estimates of effects on dust-storm days, are not based on raw data but are indeed adjusted for seasonality and the confounding effect of weather (both in the relevant caption of the relevant figure (Figure 5) as well as in the description in the text). More importantly though, we turn the reviewer’s attention to the fact that the basis of the calendar of dust-storm events was predominantly constructed based on meteorological observations. As also described above, these criteria were subsequently (and only) used to confirm, invalidate or propose additional days with the aim of categorising days into *confirmed* events (where all or most criteria were in agreement with the meteorological observations) and *suspected* events (where the criteria suggest an event that might have been overlooked by the after all subjective judgment of the observer). Since the first reviewer also requested it (see point 1 above), we have now clarified this issue further – see Identification of dust-storm days, Methods.

**Para 3:** We fully agree with the reviewer about the possibility of overdispersion, or extra-Poisson variation, in such data. To assess and correct for overdispersion, models were indeed repeated using overdispersed Poisson models (i.e. negative Binomial) and model fit was assessed by inspecting the overdispersion parameter. We have now clarified this issue in Methods, Statistical Analyses, para 1. As expected, of course, slightly wider confidence intervals were observed when adjusting for overdispersion, however, most of the estimates presented here are non-significant anyway. With regards to the main findings, at 0.83% 95%CI (0.38%, 1.28%) increase in all-cause admissions and 1.19% 95%CI(-0.1%, 2.49%) in cardiovascular admissions per 10µg/m³ increase in PM$_{10}$ the magnitude of effects and inferences remain largely unaffected by adjusting for overdispersion (Results, para 3). Finally, while we had originally only presented effect
modification by days where average temperature was lower or higher than 30°, we have now followed the reviewer’s recommendation and modified Figure 2 accordingly to include the results by days where temperature is lower or higher 20°.

**Para 4:** We have now presented average temperature by cold and warm months separately in Table 1.

**Reviewer 3:** Antonio P Ponce de Leon

**Para 1 & 2:** The reviewer summarises the objectives and methodology of the paper to highlight its original contribution, in particular with regards to the rarely investigated issue of a possible health effect of dust-storms, common in this part of the world.

**Para 3:** We agree with the reviewer that the negative effect observed with same-day levels of ozone warrants further discussion although explanations for this are not entirely clear. Negative associations with ozone were also observed in several of the 23 APHEA cities studied (Gryparis et al, 2004), which persisted even in the summer period in at least 4 of these cities (namely, Rome, Paris, Tel Aviv and Valencia). This result, not as uncommon as the reviewer also acknowledges, has often been explained as a product of the relationship between ozone (a secondary pollutant produced by photochemical reactions) and traffic-related pollutants such as nitrogen oxides (NO) and volatile organic compounds (VOC) which can reduce ozone concentrations at least at the local scale. Thus, high ozone concentrations in stations located in busy city centres, such as the one reported here, may reflect low levels or good dispersion conditions of local traffic-pollutants, that can lead to negative associations with health indicators at least in the short-run whereas it is common for stronger associations with ozone to be subsequently observed at lagged intervals. While models presented here adjust for levels of PM, with lack of data on NO and VOC concentrations, this hypothesis could not be tested further. We have now followed the reviewer’s recommendation and provided further discussion for this issue in last paragraph of the section *The effect of short-term changes in air pollutants* in the Discussion.

Furthermore, regarding the minor correction requested by the reviewer, we have now made sure that it is clear in both the caption of Figure 1 as well as in the description in the text (see **Results, para 4**) which marker represents associations with levels of ozone before and which represents estimates after adjustment for PM, namely, solid squares in the case of the first and empty squares in the case of the adjusted estimates.

Yours sincerely,

Nicos Middleton