Author’s response to reviews

Title: EFFECTS OF POLLUTION, LOW TEMPERATURE AND INFLUENZA SYNDROME ON THE EXCESS MORTALITY RISK IN WINTER 2016-2017

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Author’s response to reviews:

Reviewer 1: Peter Franklin

This study has investigated effects of various risk factors on mortality. The study design is reasonable, although more detail is required in places. The conclusions are speculative in parts and the manuscript needs some editing.

Abstract

The Abstract needs editing (as does the entire article). For example, the first sentence does not make sense. Also 'influential syndrome' is not a term - I guess the authors mean 'influenza syndrome' (this also needs to eb changed in the Introduction - lines 77 and 81, and conclusion - lines 285 and 287).

Answer: we corrected 'influential syndrome' along the text. In addition, we provided a full professional English language revision.

Abstract Conclusions

The authors cannot state that excess mortality is linked to individual choices (eg vaccination) when there are no data on vaccination for this study. Also it is not possible to say that these results can be directly related to climate change. This is pure speculation and even if there is some truth that the risk factors are affected by climate change, this study does not confirm that is the case.

Answer: we modified the abstract accordingly; in particular, all the associations to vaccinations (we instead referred to influenza epidemics) and climate change have been removed.

Introduction

Editing for this sections is also required. The third paragraph is particularly poorly organised as it starts with heatwaves and then shifts suddenly to cold temperatures. I am not sure why heatwaves are mentioned in the Introduction as this study was conducted in the European winter and the effects of cold, not hot, weather was investigated.
Answer: heatwaves were mentioned because of the reference to the Heat Health Warning System which predict extreme weather and their impact on health. However, we agreed with you and we decided to remove the hot temperature allusion from the Introduction.

The authors state that both temperature and influenza are measured as confounders in air pollution studies. Although this is correct, they are known risk factors for the outcomes of interest and have been studied as primary exposures. Therefore, the implication that they are mostly studied as confounders in air pollution studies is a bit misleading. I think the authors can suggest that they are important confounders for air pollution studies but don't imply that the only interest in these 'exposures' is as confounders.

Answer: we changed the introduction accordingly.

Methods

In the statistical analyses the authors state that 'To respond to relevant health prevention issues, we have constructed dummy variables for each exposure'. I'm not sure what 'To respond to relevant health prevention issues' means and why the exposures have to be dichotomised for that reason. Can this be explained. There is a reasonably well accepted linear (or supralinear) no threshold dose-response relationship for PM and mortality

Answer: To estimate the effect of the three risk factors on mortality we modelled the effect of each exposures as continuous variable. We completely agree with you about the PM dose-response on mortality but in addition, we proposed to evaluate the effect of the three exposure as dummy variables. This was done with the intention to better communicate at the population the risk associated to the exposures. While the risk associated to 10 μg/m3 increases in PM10 is difficult to report at the population, with these dummy variables we would like to communicate an immediate measure of risk for realistic levels, of PM10 combined with temperature, for the Po valley which is known as one of the most polluted area in Italy.

Results

I’m not sure why there is a comparison of mortality with the previous year (2nd paragraph). I don't dispute that there were increased deaths in 2016/17 but there are fluctuations in flu seasons over any number of years and a comparison just with the previous year can be meaningless because of these year-to-year fluctuations. I don't think it is necessary to include this.

Answer: we compared the number of deaths occurred in winter 2016-2017 to those occurred in 2015-2016 in order to quantify, in the ATS Metropolitan City of Milan, the alarming death excess highlighted by EURO MOMO for Europe. In fact, we find similar and concomitant peaks with that observed in many North-Western European countries. We think that comparisons with more than two years (as the other reviewer suggested) will be misleading, as you suggested, given that influenza epidemics, and its impact on the population, change every year. In fact, our principal aim was not to evaluate the effect of the three risk factor on mortality in winters but to disentangle their effects on the excess of mortality happened in winter 2016-2017.
The measurement units (eg 10ug/m³ for PM, 1C for temp and 1/103 for ILI cases) need to be included in the first paragraph where relevant results are presented, in this case the final paragraph on p9. It is confusing in that paragraph as that the authors state a 2.02% increase in mortality for PM10 but an OR of 1.002 is actually a 0.2% increase. Therefore I assume the unit of measure for the analyses was 1ug/m³ but the authors are reporting an increase per 10ug/m³.

Answer: sorry for the typo, we corrected the sentence.

I think the Figures and tables can be reduced and improved. I don't think Fig 1 is necessary and Table 2 could be submitted as supplementary material. In Table 3 I don't know what a - h stand for. There is no explanation in text or as footnote to the table.

Answer: we removed figure 1 and suggested Table 2 as supplementary material. Figure 2 has been uploaded as eps. For Table 3 (now Table 2) we included, as footnotes, the explanation required.

Discussion: What do the authors consider an inversion phenomenon (second paragraph)? Were temperature inversions measured and included in any analyses (or is it just assumed)? As with abstract the assumption of an effect of climate change is pure speculation and the results do not 'suggest' this at all. I don't mind the authors mentioning that climate change may make these interactions more likely in the future (probably toward the end of the Discussion) but it is premature to interpret the results through the prism of climate change, and spurious to do so from a single study.

Answer: we modified the discussion accordingly, removing the suggestions of an effect of climate change. We rather suggested (at the end of the Discussion) an interest in estimating the mortality excess, occurred in winter 2016-2017, attributed to climate changes.

The 7th paragraph (from line 255) gives an explanation that suggests a threshold for PM10 (70 μg/m³) (I think that is what is suggested). However, this is contrary to current understanding of the dose-response relationship between PM and mortality. I reiterate my concern about dichotomising the continuous variables. It would be better to investigate the shape of the dose-response curve using the continuous data

Answer: as previously discussed, in this study, in order to investigate the shape of the dose-response curve, we provided results in terms of continuous exposures. In addition, we further decided to estimate the effect on mortality using dummy variables to evaluate extreme levels of air pollution that are not uncommon in the Po valley.

Last paragraph - it is difficult to make any conclusions about vaccination when the data for individuals are not available for the study and could not be controlled in the analyses.

Answer: we modified the Conclusions section on vaccination suggesting that vaccination coverage of elderly persons will continue to be the primary strategy for preventing influenza-associated deaths.
Reviewer 2: Aabid A. Ahmed, Ph.D

Abstract
Please explain what is influential syndrome.

Answer: we are sorry for the typo, we modified influential syndrome with influenza epidemics along the text.

In the results section the word where should be replaced with were. In the methods section, there is no mention of vaccination. It is introduced in the conclusion. The conclusion can only conclude what is being studied.

Answer: thank you very much for these corrections. We modified the abstract accordingly; in particular, we removed all the associations to vaccinations (we instead referred to influenza epidemics).

The number of tables can be reduced by either combining some or reducing.

Answer: we suggested Table 2 as supplementary material (as suggested by the other reviewer).

It may be good to compare data over a few years than simply comparing it over two years and drawing conclusions from this.

Answer: we compared the number of deaths occurred in winter 2016-2017 to those occurred in 2015-2016 in order to quantify, in the ATS Metropolitan City of Milan, the alarming death excess highlighted by EURO MOMO for Europe. In fact, we find similar and concomitant peaks with that observed in many North-Western European countries. We think that comparisons with more than two years (the other reviewer suggested instead to remove the comparison at all) will be misleading given that influenza epidemics, and its impact on the population, change every year. In fact, our principal aim was not to evaluate the effect of the three risk factor on mortality in winters but to disentangle their effects on the excess of mortality happened in winter 2016-2017.

The conclusion seems to be too general. This needs to be revised and make it specific to the study.

Answer: we modified the discussion and the conclusion sections.