Reviewer's report

Title: Hourly Differences in Air Pollution and Risk of Respiratory Disease: a time-stratified case-crossover study

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MAJOR REVISIONS

Methods

The case-crossover description mixes some basic information about the study design (such as that it uses cases only and that it compares the exposure before events with other exposure periods) with a perhaps excessively summary description of how the authors selected the control periods. This description could even be misleading, as it does not make clear whether the control periods were chosen on other days as they were for the 24-hour periods (the metric used by the authors who introduced the time-stratified approach of case-crossover [Maclure, 1991; Lumley 2000]) or on the same days. For the first hypothesis, the authors should state whether they selected as controls the same six-hour intervals on other days as those on which the case occurred; for the second hypothesis, the control periods would be the six-hour intervals preceding and following the six-hour case period within the same day; this is important in relation to the potential confounding by the circadian pattern of the respiratory outcome the authors studied [Peters 2001]. I suggest that the authors explain these points more clearly. On the other hand, to explore the hourly effects within a whole day, I would suggest that the authors cover different lag periods within the same day, as previous studies have done [e.g. Bhaskaran 2011]: for example 7-12, 13-18, 19-24, rather than analysing 12-hour intervals that overlap the 0-6 period.

Misclassification of exposure is, however, more than likely when individual exposure assessment cannot be carried out; it has been shown in a re-analysis of the six-city study that only a buffer no greater than 5 kilometres could provide a reliable approximation of exposure to the individual addresses. Moreover, the authors maintain that no hourly data are missing for any of the pollutants they studied or for temperature and humidity. I take the liberty of declining to believe this, since they were studying a 5-year period and as many as 11 monitoring stations. Maybe the authors mean that the values were all imputed, but if that is the case, I would like to be told how they imputed the missing values among the stations, the days and the hours of the same day. This is particularly important because they analyse hourly differences in exposure and the probability of missing data however sparse and although imputed could affect the estimates more than in 24h periods.
Meteorological factors were entered in the analyses with different dfs, selected apparently a priori. I think the authors should have explained this choice, since the apparent temperature (combining T and H) has been used in many other studies. Moreover, it is not clear whether the spline they used for temperature and humidity in the periods shorter than 24 h had the same degree of freedom as those they used for 24h periods.

No rationale has been given by the authors for having selected over-65-year-olds, when important effects of air pollutants have been reported, in the scientific literature, for children and adolescents.

The authors studied respiratory outcomes (all, COPD, pneumonia and influenza). They also used medical histories for information about comorbidities, so as to analyse their possible role as effect modifiers. Many questions arise about the health data. The first has to do with their source of information. The outcome of the studied association is defined (in Background, p. 5) as the risk of respiratory disease onset in residents who made ER visits. However, the analysed data refer to people who got to hospital by ambulance, which could have introduced a selection that excluded people who arrived for emergency services by their own means. Moreover, we do not know if the diagnosis the authors used was made in the emergency room or by “physicians at the hospital” (as is stated in Methods, p. 6), which could mean during a hospitalisation. This point could affect diagnosis reliability, since there would be a difference between those who made only the an ER visit and those who received a hospital diagnosis, or it could bring about another selection of people, if only those hospitalised following their ER visit and for whom a hospital diagnosis was made, were included.

Another problem concerns influenza: we read that influenza was used, together with pneumonia, as a possible outcome of exposure; yet again these data were not obtained from ER visits, but instead from public health surveillance. If this is the case, I wonder whether the dual source could have given rise to a non-comparability of the two groups: cases of influenza treated at home and included in the surveillance and cases of other diseases, and even influenza, who have recourse to emergency rooms. I also wonder how the time of onset was assessed for the influenza cases who did not get ERV, and why the authors assume that air pollutants could induce influenza; while pneumonia could be the result of an irritation due to chemical substances (especially gases), respiratory infections are more likely to be a consequence of environmental exposure at an early age, especially in asthmatic children. Finally, if the diagnoses of comorbidity came from ER, how confident are the authors about the reliability and completeness of this information? Now, a sensitivity analysis could resolve the first point as well as the last by analysing pneumonia without influenza. However, the source of the diagnosis and the time of influenza onset require a clearer definition. Incidentally, I have assumed that “onset” refers to respiratory symptoms or syndromes and not to incident diseases.

Results
health data Table 1 should report data relative to possible selections of participants as well as the number of patients with no previous diseases and of those for whom information about previous diseases was not available. It seems surprising that only 11% of respiratory diagnoses refer to COPD (the authors also include asthma) in this older population, when COPD emergency hospitalisations generally show values ranging from 25% - 30%. Could the authors check this datum?

environmental data Table 2 shows a very high standard deviation for the mean hourly values of pollutants, which in turn causes high IQR for all the pollutants. I suggest that the authors stratify these values into three or four daily time periods, to see how hourly pollutant levels change at different periods of the day (for example: morning, afternoon, night), which would seem to support the advisability of exploring different lags (as I proposed above) or of stratifying the analysis according to different periods of the day. The correlation coefficients (CC) are also lower than those found in earlier studies, especially for SPM and NO2. A recent review found CC between NO2 and PM10 ranging between 0.5-0.9 and CC up to 0.88 between NO2 and PM2.5. I actually remember a recent study from Japan [Katanoda 2011] that reports a CC as low as 0.3 between NO2 and PM2.5, although for annual data. Have the authors an interpretation for this?

Discussion

My first general comment concerns a pair of important omissions: the authors do not discuss the negative results and especially how the analytical methods could have affected the results. For example, most studies in a recent review [Bentayeb 2012] of air pollution and respiratory hospitalisations in the elderly, reported important effects on COPD, but the authors apparently did not observe any. On the other hand, many ill-defined steps in carrying out the analyses could have influenced their results, such as the possible misclassification of exposure, the possible selection of patients and choosing to analyse the shorter periods within a day.

Secondly, the references are sometimes dated.

Coming to more specific comments,

- although it is possible to agree that working on hourly pollution data and using individual information are among the strengths of this study, I cannot agree that this is the only study that has found effects on acute respiratory events. I suggest that the authors check more recent references than the 1st and 2nd on their list and that they avoid ambiguity between new respiratory events and incident respiratory diseases. Moreover, though most previous studies deal with a daily metric of short-term effects, others use an hourly metric and, by comparing them this study does not support the idea that the authors have here introduced an exact temporal definition: indeed the authors list not having the exact times of disease onset among the limitations of their study.

- The authors actually do discuss the possible misclassification of diagnosis. However their
comments risk being misleading, since they refer the problem to the diagnostic ability (which could in fact be assumed to be higher in larger hospitals) of the emergency departments, but differential misclassification relates to a systematic difference of diagnosis between exposed and unexposed subjects. On the other hand, even if misclassification is rare, it does not depend on diagnostic ability, but instead on the difference in diagnostic protocols between the emergency room and the wards.

- The Berkson bias is inappropriately cited, since it should properly refer to the possibility that both those exposed to risk and those suffering from respiratory symptoms have recourse independently to emergency room visits, whereas the authors are discussing the different impacts that random and systematic errors cause on estimates.

In conclusion, I think the authors should produce a carefully revised version so that the manuscript can be reconsidered for publication.

Level of interest: An article of importance in its field

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

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests