Author’s response to reviews

Title: The association between daily concentrations of air pollution and visits to a psychiatric emergency unit: A case-crossover study

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Author’s response to reviews:

Dear Editor and Reviewers

We sincerely thank you for the extensive comments on our manuscript, which we think have led to major improvements. We hope you will find the manuscript in order.

Yours sincerely

Anna Oudin, on behalf of all co-authors

Reviewer #1: Review of Oudin et al.

This is a generally well done analysis of the association between air pollutants and psychiatric emergency room visits. This is an important topic and one that needs more analyses such as these. I have a few points to address, though:
Major points:

In "Materials and Methods: Data": The authors mention that a minority of the psychiatric emergency visits are for things like prescription refills rather than emergencies. This is a very important point as too many of these kinds of visits could raise the possibility that associations are not specific for emergencies. Is there any actual data on how many are this kind of thing? That should be reported, and even possibly a sensitivity analysis done to show what kind of effect size there would be if all the effect was on these kinds of visits rather than true psychiatric emergencies.

Answer: We fully agree. Unfortunately we do not have data on the reason for the visit, or on diagnosis, which is a limitation of the study. The Clinical psychiatrist co-authors (SS and ZS) estimate that the proportion of visits who are due to prescription refills and similar are less than 5% and probably more like 2% on any given day. We have elaborated on this limitation in the discussion. We think however, that even if a visit is not a “true” emergency visit, but a visit for prescription refill it is most likely associated with worsening in some sense (following the same logic as studies on short-term effects of air pollution on dispensed medications).

2) In the second paragraph of the discussion, there is a section on the possible problems with exposure misclassification. I don't believe the arguments being made are quite correct. The error that is being described is in how well the monitor data predicts the actual personal exposure. In this scenario, the personal exposure is a collider (in Directed Acyclic Graph terminology) between the monitor exposure measure and personal behaviors like how much time one spends indoors vs. outdoors. In this case those personal behaviors cannot confound the estimate of monitor exposure levels. Measurement error (how well the monitor level predicts personal exposure) can lead to a reduction in the effect estimate for the monitor levels (assuming the effect is through personal exposure), but only if there is actually a true association between personal exposure and the outcome, and the bias will be towards the null (see Weisskopf et al., Curr Environ Health Reports, 2015 and Weisskopf and Webster, Epidemiology, 2017 for related issues).

The story is a little different if monitor levels of the pollutants affect behavior. This could then be a "non-biological" way the pollutant affects the outcome. If pollutants are really related to the outcome, and if high monitor air pollution leads people to stay inside (and so not have as much actual exposure), then the association could flip with higher levels looking protective. But it couldn't create a false positive association since if there was no real association, then how well the monitor levels predict personal exposures is irrelevant as there is no effect of personal exposure. (There is the theoretical possibility that it could inflate a real association, but only if lower monitor pollutant levels made people stay inside more than higher pollutant levels and that seems unlikely).
If the argument is that monitor levels of pollutants affect whether people go to the emergency room, and so become a case (for reasons other than a true effect of the pollutant on biology leading to case status), then one could get a false positive association if high monitor pollution days were associated with people going to the emergency room more than on low pollution days. This could occur by simple confounding of the monitor pollutant level. And the authors have attempted to address this by adjusting for things like temperature and other pollutants. Maybe there are things like that that they have missed, but this falls under the category of residual confounding. If high pollutant levels at the monitor somehow directly led to people going to the emergency room (by some means other than a biological effect of the pollutant leading to mental health issues), then a positive association would be seen. I suppose this could be mentioned, but at the same time pointing out that this seems unlikely would seem warranted to me.

A bias away from the null could occur if there was an overestimate of pollutant levels at the monitor on days with more emergency visits than on days with fewer emergency visits, but that seems very far-fetched.

In sum, I think measurement error could not produce a false association unless somehow monitor pollutant levels were overestimated on emergency room visit days (or underestimated on control days, which seems far-fetched to me). Bias from personal behavior (not driven directly by the monitor level of the pollutant—or something confounding it) should not account for the finding based on arguments similar to those in the papers mentioned above. That residual confounding—perhaps most likely by some other pollutant—could account for the association is certainly possible and should be mentioned (but it would have to be by something that varies on the order of weeks). But I think as this is currently written in the manuscript incorrectly calls more question into the results than is warranted.

Answer: We sincerely thank the reviewer for this elucidating comment, and we have corrected our mistake and added a few references.

Minor points:

1) Abstract, results: In the last sentence, indicate that "during winter" applies to the PM results.

Answer: Thank you for pointing that out, it has been corrected.

2) Something is wrong with the wording of the third sentence of the "Psychiatric emergency visit (PEV) data" section.

Answer: Thank you for pointing that out, it has been corrected.
3) Statistical methods: It is stated that four control days per PEV were used, selected as the other same days of the week within the same month. But what if the PEV day was in a month with only four of those days? Wouldn't there be many cases of only 3 control days?

Answer: Thank you for pointing that out, it has been corrected.

4) Results: Please also show pollutant levels by season, since some of what you do is specific to season.

Answer: We agree and we have added descriptive data stratified by season (Table 1).

5) Discussion: the second paragraph is extremely long and contains many points. This could be broken into more paragraphs.

Answer: we think there must have been a mistake, because the second paragraph didn’t seem that long to us, but we have restructured the entire discussion, so that no paragraphs should be too long.

6) Discussion 2nd paragraph: The sentence that begins "A strength of time-series…” later should read: ")…, is that the risk OF residual confounding from TIME INVARIANT individual…”

Answer: Thank you for pointing that out, it has been corrected.

7) Same paragraph sentence beginning "However, there could…": Since control days are from within the same month as the PEV day, how could season possibly still confound? Meteorological yes, but only those that vary on a weekly basis.

Answer: Pollen is the only (possibly relevant example) we could think of, we clarified the text.

8) Further down in the same paragraph the discussion of the seasonal differences: another possibility is that the dose-response is not linear and one is at a different place on the dose-response curve in winter and summer. It seems a little unlikely that exposures are higher in the summer, but this is why showing pollutant levels by season in the results is important.
Answer: We agree and we have added descriptive data stratified by season (Table 1). There are no large differences in concentrations during the warm and cold season in the study area.

Reviewer #2: Review

The association between daily concentration of air pollution and visits to a psychiatric emergency unit: A case-crossover study

The topic itself is very interesting. It will need much more research in the future.

I have the following questions:

Abstract

I would propose to be a bit more cautious as we are not sure whether air pollution is affecting mental health and not "how it is affecting mental health". What is meant by mental health? What are mental health problems? It would be clearly distinguish between mental health (as a positive state), mental health problems (please define) and mental disorders.

Answer: We had a lot of discussions in our group on how to denote our outcome in the present study. Since we do not have access to diagnoses, or type of visit, we decided upon mental health problems, but we agree that it is very vague. We have now changed the wording to “psychiatric disorders and mental distress”, which is longer, but more appropriate.

Was there an association or "seemed to be an association?"

Answer: There was an association (statistical significant) in the single-and two-pollutant models, but in the three-pollutant models the p-value was slightly above 0.05. The effect estimate for PM10 was very similar in all models, though, so we think we could say that there actually was an association. We may have been too conservative stating that there “seemed” to be an association, and we have now removed that word.

Introduction

Please specify and clarify what you mean by "Mental Health". Mental Health is defined as a positive state of mind. I wonder why in the first sentence authors speak about mental health and
in the second sentence about depression. Please clarify whether you mean depression or mental health. Do you mean "mental health problems" of mental disorders?

Answer: Same as above: We had a lot of discussions in our group on how to denote our outcome in the present study. Since we do not have access to diagnoses, or type of visit, we decided upon mental health problems, but we agree that it is very vague. We have now changed the wording to “psychiatric disorders and mental distress”, which is longer, but more appropriate.

Methods/Results

Methods and results are well described, however language should be checked. Did you conduct a sample size calculation? The results are marginally significant - I would be interested in power calculations. Likewise maybe an sensitivity analyse according to diagnoses could be done?

Answer: Thank you. We had the manuscript checked by a native speaker. We did not do a sample size calculation, and we agree that statistical power is probably too low in the present study. The reason for not calculating statistical power was that we had access to already available data, which we could use before we start the long process of applying for more detailed data on age, sex, type of visit, diagnoses. It will take a long time to get more detailed data (applying for funding, ethical vetting, applying for the data). Given the very limited number of studies in this area, we think that the current results are very interesting even though we would like to have had more detailed data of the type we just mentioned. Furthermore, the results are a strong warrant for future research in this area.

Discussion

Please discuss limitations of the study. Please specify what you mean with "warm weather". Higher temperatures have been associated in other studies with increases in some mental disorders. Could the change in temperature be a further possibility of explanation? The limitations of this study using routine data should be clarified.

Answer: We have rewritten, and expanded, the limitation section in the discussion. We have defined what we mean with warm season in several places in the text.
Reviewer #3: Review of "The association between daily concentration of air pollution and visits to a psychiatric emergency unit: A case-crossover study"

The paper provides a case-crossover analysis of the association between short-term exposure to air pollution and psychiatric emergency visits in Sweden. The study objective is not novel as there has been existing literature on similar topic. The findings are mostly insignificant and inconsistent, especially when the authors only had very limited information on the psychiatric emergency visits that hindered the authors from carrying out more in-depth analyses. I acknowledge the authors for being transparent about the many study limitations in the discussion. Nevertheless, the main question remains as whether there is any new evidence from the current study that can add to the current knowledge on the association between air pollution and mental health, which I don't think so.

Answer: We thank the reviewer for the comment, but we disagree that the study objective is not novel. Compared to the thousands of time-series studies on air pollution and physical health outcomes, the number of epi studies on outcomes on mental health is extremely small. Our experience is that there is a lot of scepticism towards this research area, and we therefore think that it is very important to publish available data, despite certain limitations, to increase awareness that there may be associations not only between air pollution and physical health, but also with mental health/illnesses. If there are relevant references we have missed however we would be most grateful for any tips. As the Reviewer acknowledges, we have tried to be very transparent about the limitations of our study. We think it is important to stress that our study has many limitations in common with many other studies with similar design. We have also highlighted strengths of the study, and given the few studies in this field we think that our study is important.

Specific comments:

* Can the author elaborate on the representativeness or generalization of the study population to the entire Gothenburg population? Did the authors have additional information on the psychiatric visits (e.g., age, gender) that can be used in the effect modification analysis? Although the authors listed these as limitations later in the discussion, it would be better to put such information in the method section as well.

Answer: Unfortunately, we do not have any additional information, age, gender, diagnosis. We have mentioned that in the method section now to make it clearer. We have also elaborated on the representativeness of the study population.
* Why the authors opt for case-crossover analyses versus time-series analysis? Although both have their pros and cons, but in general time-series analysis tends to provide more precise risk estimates than those from the case-crossover study.

Answer: As the reviewer points out there are pros and cons with both methods of analyses. We state in the methods section that we did not analyse the data using a conditional logistic regression which may be the most used statistical method for analysing case-crossover studies. Instead we used a time-series approach, we ran a conditional Poisson regression allowing for over-dispersion with a stratum variable indicating day-month-year was included.

* Did the authors control for days of week in the models?

Answer: The case-crossover analyses does so by design.

* I can see from Figure 1 that there were some gaps in PM10 and O3 levels. How the authors handled missing data is unclear, and need to be clarified further. I would suggest the authors to impute the missing data.

Answer: Yes, there were some missing data (also shown in Table 1). We ran complete-case data only in the submitted version of the manuscript, but in the revised version we have added a sensitivity analysis where missing PM10-values were imputed. PM10 was the pollutant where the largest proportion of observation were missing, and the only pollutant with which we observed associations with the outcome. The results with the imputed data were very similar to the complete-case analysis. For the whole year data, the increase in PM10 ranged between 1.7% to 2.4%, and when pooling the estimates, the increase was 2.0%, which is close to the 2.1% increase we obtained in the complete case analysis (all year estimate).

* I would use IQR instead of 10ug/m3 across all air pollutants, so you would not unrealistically inflate the effect estimates for PM10 to 10 when the normal fluctuation was about 6, or deflate that for O3.

Answer: We agree, the IQR is relevant. We decide to use an increase of 10ug/m3 across all pollutants for comparison reasons. However, we have added the IQR results to the Supplementary Table 1.

* Had the authors considered modeling the 3- to 7-days moving averages or cumulative lag exposure, as the association of psychiatric visits with air pollution maybe semi-chronic, as
shown in Pun VC, Manjourides J, Suh H. Association of Ambient Air Pollution with Depressive and Anxiety Symptoms in Older Adults: Results from the NSHAP Study. Environ Health Perspect. 2016;125(3):342-348 (also a good reference to cite).

Answer: Yes, there are several studies now suggesting that there may be associations also with chronic exposure and psychiatric disorders. However, this should not bias our estimates since we’re, in this study, interested in contrasts over time.

The associations we observe are solely in lag 0, and the cumulative lag exposure (3 or 7 days) are not statistically significant, and the association estimates are weaker. We have now added this information to the manuscript.

Minor comments:

* Define acronyms e.g., "OECD", "GDP" in the beginning.

Answer: We have revised the manuscript accordingly.

* Please use punctuation properly. Long sentences need to be separated by comma, or else it is difficult to read.

Answer: We have revised the manuscript to avoid too long sentences.

* Be caution when using the causal language because this type of study cannot answer such causal question. You may want to temper the causal language throughout the manuscript (e.g., change "acute effect of air pollution on worsening of mental health" on line 10 to "association between acute exposure to air pollution and mental ill health").

Answer: We have revised the manuscript accordingly.