Author’s response to reviews

Title: Low concentrations of fine particle air pollution and mortality in the Canadian Community Health Survey Cohort

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Author’s response to reviews:

Comments from both reviewers

1. Explain attenuating effect of O3 and NO2 and contrast with other studies, convince readers of the primary role of PM2.5 despite these findings

We have included text to address the observed findings of the multi-pollutant models (pg. 18):

These findings indicate both that PM2.5 is associated with mortality and that the inclusion of gaseous co-pollutants, Ox in particular, may better characterize the biologically active aspects of
PM2.5 and the overall air pollution mixture compared to the PM2.5 mass concentration (5). Weichenthal et al. looked at the effect modification of oxidant gases on PM2.5 more specifically and found that spatial variations in Ox concentrations may act as surrogates for the presence/absence of harmful air pollutant mixtures that enhance PM2.5 toxicity (37). We examined the PM2.5 mortality association in both low- and high- Ox person-years and found a 24% difference in risk. Our findings support these previous studies using different longitudinal Canadian cohorts and that knowledge of interactions between PM2.5 and oxidant gases leading to adverse health will improve risk management activities and public health.

2. Mention the specific causes of death for the non-accidental deaths

We will be looking at specific causes of death and their relationships to PM2.5 exposure in future work. We have included detail about what the main causes of death were within the cohort (pg. 11):

There were 50,700 non-accidental deaths. Of these, there were 7,900 deaths from ischemic heart disease, 2,800 from cerebrovascular disease, and 4,300 from other cardiovascular diseases; 900 from pneumonia, 2,800 from COPD, and 1,100 from other respiratory diseases; 5,500 from lung cancer, 1,300 from colon cancer, 1,300 from breast cancer, 1,100 from pancreatic cancer, and 9,900 from all other cancers. Further, there were 1,700 deaths from diabetes, 3,900 deaths from neuropsychiatric conditions, 2,200 from digestive diseases, 1,100 from genitourinary diseases and 3,000 from all other non-accidental causes.

Reviewer 1

3. Ensure that the purpose in the abstract and the manuscript are describing the same thing

The abstract has been revised to better align with the manuscript (pg. 2):

Background: Approximately 2.9 million deaths are attributed to ambient fine particulate air pollution around the world each year (PM2.5). In general, cohort studies of mortality and outdoor PM2.5 concentrations have limited information on individuals exposed to low levels of PM2.5 as well as covariates such as smoking behaviours, alcohol consumption, and diet which may confound relationships with mortality. This study provides an updated and extended analysis of the Canadian Community Health Survey-Mortality cohort: a population-based cohort with detailed PM2.5 exposure data and information on a number of important individual-level behavioural risk factors. We also used this rich dataset to provide insight into the shape of the concentration-response curve for mortality at low levels of PM2.5.
4. Include data from non-CCHS based studies in the discussion

Throughout the discussion we have added comparisons to other similar studies (especially those with individual level behavioural risk factors) and deepened the contrasts made between the current findings and the already referenced works.

e.g (pg. 15):

The hazard ratio for the full cohort was similar to that of the Nurse’s Health Study in the United States (1.13 95% CI 1.05-1.22) that adjusted for individual-level socio-economic and behavioural covariates (38) and a cohort from England (1.13 95% CI 1.00-1.25) that controlled for smoking, BMI, income, age, and sex (40). Burnett and colleagues (39) report hazard ratio estimates for a 10 µg/m³ change in long-term exposure to PM2.5 and non-accidental mortality in 41 cohorts conducted globally, 36 of which included adjustment for behavioural risk factors. The pooled hazard ratio among these 36 cohorts was 1.09 (95% CI 1.05-1.12), a value similar to that observed in our current study (1.11 95% CI 1.04-1.18). A version of the 2001 CanCHEC census-based cohort, which began prospectively in 2001 and is more comparable to this study, produced a hazard ratio that is similar to this work (1.09 95% CI 1.07-1.11) (6).

e.g (pg. 20):

The CCHS over-samples rural communities which results in a disproportionate sample in areas with low levels of PM2.5 and higher rates of mortality. The sampling framework and un-weighted analysis likely caused the null unadjusted hazard ratio which became positive as covariates were added to the model to address confounding. These results are consistent with the Agricultural Health study which examined non-accidental death related to PM2.5 in rural communities in two American states (Iowa and North Carolina) and found a protective hazard ratio in minimally and fully adjusted models (56).

5. Explain why inclusion of behavioural covariates led to a decrease in the hazard ratio

This has been addressed (pg. 15):

The inclusion of behavioural covariates to a model including socio-economic and ecological covariates lowered the PM2.5 hazard ratio 2% (from 1.13 to 1.11). This modest change in the hazard ratio can be interpreted as an indicator of behavioural covariates being adequately controlled for by the socio-economic and ecological covariates in the established relationship between PM2.5 exposure and non-accidental mortality.

6. Discuss the relevance of the SCHIF shape to public health
Previous work using a CCHS-based cohort used a spline-based procedure and found that the shape of the relationship between non-accidental mortality and PM2.5 was supra-linear in shape with a threshold of 4.5 μg/m3, but was limited due to wide confidence intervals (9). A study in China using a SCHIF function found non-linear relationships for multiple causes of death (43). The SCHIF functions suggest risks to concentrations below 2 μg/m3. Such a relationship, when applied in a health impact framework, as in the Global Burden of Disease (44,45) and in the recent Global Exposure Mortality Model (41) suggest benefits both from reducing PM2.5 concentrations areas with the highest concentrations and from continuing to reduce them in relatively cleaner areas, including Canada, where it is estimated that the entire population now lives in areas with ambient PM2.5 concentrations below the current WHO Guideline (46). Worldwide it is estimated that small absolute reductions under 3µg/m3 could prevent hundreds of thousands of deaths in areas that comparatively have low levels of PM2.5 (47).

Reviewer 2

7. Discuss why the unadjusted hazard ratio was protective and why it evolved to be significant after adjustment

It may be that the unadjusted model produced a protective hazard ratio because of oversampling in rural communities, which further supports the importance of adjusting for covariates. We included further detail about the CCHS and its limitations which may explain this (pg. 20):

The CCHS over-samples rural communities (55) which results in a disproportionate sample in areas with low levels of PM2.5 and higher rates of mortality. The sampling framework and un-weighted analysis likely caused the null unadjusted hazard ratio which became positive as covariates were added to the model to address confounding. These results are consistent with the Agricultural Health study which examined non-accidental death related to PM2.5 in rural communities in two American states (Iowa and North Carolina) and found a protective hazard ratio in minimally and fully adjusted models (56). Regardless, the protective unadjusted hazard ratio should not come as a surprise as contextual and socio-economic covariates are included in models because we know that they are related to both PM2.5 and mortality and can act as confounders (see Table 1 for the mortality Hazard Ratios by individual covariates). Given that these factors covary with both mortality and PM2.5 their inclusion in the models is crucial. We suggest that the unadjusted model is not reflective of the PM2.5 -mortality relationship and that the direction or magnitude should not be over-interpreted.
8. **Explain why educational attainment does not share the same relationship to PM2.5 exposure as income**

This has been added to the paper (pg. 16):

These results are consistent with descriptive analysis of PM2.5 exposure in 2006 long-form census respondents (9). Although urban areas are the most common residence for both high income and highly educated Canadians, rural residences are more common among the high income earners than university graduates (i.e. within the highest income quintile, 73.7% urban vs 26.3% urban fringe or rural; among those who are university educated, 82.6% urban vs. 17.3% urban fringe or rural). The greater tendency for high-income Canadians to live in rural areas is consistent with the findings in this paper. As a result, PM2.5 exposure by income categories is a slightly more linear pattern than education in both of these studies.

9. **Explain why being a regular drinker was a negative confounder**

As seen in Table 1, regular or occasional non-binge drinking appears to have a protective effect on mortality but these groups also have higher exposure to PM2.5 compared to other categories. Additional analysis of effect modification found in Table 4 indicates that in the relationship between PM2.5 and mortality, the regular and occasional drinkers are at a significantly higher risk of death compared to the never or former drinkers (Cochrane’s Q 5.1, p=0.02). An explanation for this is provided (pg. 15):

This finding is similar to the previous CCHS cohort analysis and analysis of a Medicare-based cohort; both reported that adjustment for behavioural covariates had a minimal effect on hazard ratios (3,7). There is evidence (Tables 3 and 4) for a small increase in risk of PM2.5-related mortality in occasional or regular drinkers but this may be masked by null effects from the inclusion of other behavioural covariates (fruit and vegetable consumption, smoking behaviours) and this confounding is likely the result of the spatial distribution of drinking behaviours, with binge drinkers having the largest mortality risk but lower PM2.5 exposures.

See also Response #11.

10. **Discuss why airshed is associated with mortality and the possible mechanism**

We have included additional text regarding the impact of airsheds on the hazard ratios (pg. 16):

The increase in the PM2.5 hazard ratio with the addition of the ecological covariates was largely driven by the addition of airsheds. Not only do these airsheds characterize broad air movement patterns, they also capture areas with similar composition of PM2.5 (e.g., proportion of PM2.5 composed of nitrate is highest in the Prairie airshed, whereas the Southern Atlantic airshed is
composed of a notably higher proportion of black carbon) (34). They also delineate general socio-cultural groups with distinct mortality risk factors beyond those captured by the typical socioeconomic census variables included in our survival models. The three airsheds with the largest hazard ratios, along with high material deprivation, all have the lowest levels of air pollutants which would account for the negative confounding effect observed in Table 3. Further, the largest airshed (East Central) contains both Toronto and Montreal, the two largest CMAs in Canada and significant population hubs. High PM2.5 exposure and related mortality are largely driven by the population of Toronto (21% of the national population in 2006) where the mean PM2.5 exposure is 9.33 μg/m3 whereas the mean in the rest of the country is 7.68 μg/m3 (43).

11. Explore the data with further stratified analysis for airshed, education, and behavioural covariates

We performed additional stratified analysis by the behavioural covariates (fruit and vegetable consumption, alcohol consumption, and smoking) and educational attainment (pg. 14):

There was no significant difference between those who consumed fewer than five servings of fruits and vegetables per day compared to those who consumed five or more (1.10 95% CI 1.01-1.20 vs. 1.16 95% CI 1.04-1.30) although the hazard ratio was higher for those who consumed more fruits and vegetables. We found that hazard ratios are higher for regular drinkers (1.18 95% CI 1.09-1.28) and daily or occasional smokers (1.13 95% CI 0.99-1.27) compared to never or former drinkers (1.01 95% CI 0.90-1.12) or never or former smokers (1.11 95% CI 1.03-1.20), with a significant difference found between those who do and do not consume alcohol (p<0.05).

And interpret these findings in the discussion (see also response #9) (pg. 18):

We examined effect modification by behavioural covariates (i.e., fruit and vegetable consumption, smoking behaviour, and alcohol consumption) and found significant difference in the resulting hazard ratios only in the case of alcohol consumption. Effect modification analyses on the ESCAPE cohort also found no effect modification by fruit and vegetable consumption or smoking behaviour, but did not consider alcohol consumption (2).

We did not perform additional stratification by airshed. Since a significant majority of Canadians live in the East Central airshed it is of limited utility to stratify by this variable as the remaining airsheds have too few respondents. Merging these remaining groups would mask the spatial nature of the variable.

12. Explore the robustness of the association between PM2.5 and mortality and low levels
We appreciate this insight. An analysis of low exposure groups is part of our analytical plan and will be featured in an upcoming paper. This analysis will entail building different models for different exposure sub-groups and comparing lifetime exposures vs specific exposure windows. Given the complexity of these analyses and the many additional models required, we feel that it is beyond the scope of this paper which profiles the cohort and would be better-suited elsewhere.