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Impact of Oxidant Gases on the Relationship between Outdoor Fine Particulate Air Pollution and Nonaccidental, Cardiovascular, and Respiratory Mortality

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Outdoor fine particulate air pollution (PM_{2.5}) is known to increase mortality risk and is recognized as an important contributor to global disease burden. However, less is known about how oxidant gases may modify the chronic health effects of PM_{2.5}. In this study, we examined how the oxidant capacity of O₃ and NO₂ (using a redox-weighted average, O_x) may modify the relationship between PM_{2.5} and mortality in the 2001 Canadian Census Health and Environment Cohort. In total, 2,448,500 people were followed over a 10.6-year period. Each 3.86 µg/m³ increase in PM_{2.5} was associated with nonaccidental (Hazard Ratio (HR) = 1.095, 95% CI: 1.077, 1.112), cardiovascular (HR = 1.088, 95% CI: 1.059, 1.118), and respiratory mortality (HR = 1.110, 95% CI: 1.051, 1.171) in the highest tertile of O_x whereas weaker/null associations were observed in the middle and lower tertiles. Analysis of joint non-linear concentration-response relationships for PM_{2.5} and O_x suggested threshold concentrations between approximately 23 and 25 ppb with O_x concentrations above these values strengthening PM_{2.5}-mortality associations. Overall, our findings suggest that oxidant gases enhance the chronic health risks of PM_{2.5}. In some areas, reductions in O_x concentrations may have the added benefit of reducing the public health impacts of PM_{2.5} even if mass concentrations remain unchanged.

Numerous studies have documented the relationship between long-term exposure to outdoor fine particulate air pollution (PM_{2.5}) and mortality and these pollutants are recognized as important contributors to global disease burden¹. However, PM_{2.5} is only one component of complex air pollution mixtures and it is not clear how/if the magnitude of PM_{2.5} health risks depend on concentrations of oxidant gases. This is an important question as populations are simultaneously exposed to *both* PM_{2.5} and oxidant gases (e.g. O₃ and NO₂) but it is not clear how the chronic health risks PM_{2.5} may depend on these other pollutants.

Crouse *et al.*² recently examined multi-pollutant and cumulative-risk models for the relationship between PM_{2.5}, NO₂, O₃, and non-accidental mortality and noted positive associations for all three pollutants; however, this study did not specifically evaluate how these oxidant gases may modify the chronic health effects of PM_{2.5}. Nevertheless, existing evidence suggests that such effect modification is biologically plausible. For example, elevated O₃ concentrations are known to deplete anti-oxidants in the lung lining fluid³ and increase the permeability of the lung epithelium⁴⁻⁷. Therefore, PM_{2.5} exposures may be more harmful in regions with increased levels of oxidant gases owing to decreased oxidant defense at the initial site of pulmonary deposition as well as a more permeable lung epithelial barrier.

In this study, we evaluated the extent to which oxidant gases may modify associations between outdoor PM_{2.5} mass concentrations and non-accidental, cardiovascular, and respiratory mortality in a large population-based cohort of Canadians. Our primary interest was in evaluating how the *combined* oxidant capacity of these gases (calculated using their redox-weighted average (O_x), described below) may potentiate PM_{2.5} health effects.

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Results

Participant characteristics are summarized in Table 1. In total, 233,340 non-accidental, 77,000 cardiovascular, and 21,100 respiratory deaths were observed during the 10.6-year follow-up period. As expected, residential estimates of outdoor air pollution concentrations across Canada were low (Table 2) with PM_{2.5} concentrations ranging from approximately 1 to 20 µg/m³ with a mean value of 7.37 µg/m³. PM_{2.5} and O_x were moderately correlated ($r = 0.66$). Spatial variations in NO₂, O₃, O_x, and PM_{2.5} across Canada are shown in Supplemental Figures S1–S4.

Single Pollutant Models. All four pollutants (PM_{2.5}, NO₂, O₃, and O_x) were associated with increased non-accidental, cardiovascular, and respiratory mortality in single pollutant models including linear terms for each pollutant (Table 3). Hazard ratios for O_x were generally higher than for O₃ or NO₂ individually except for respiratory mortality which was similar to that for NO₂. For PM_{2.5}, analyses across tertiles of O_x suggested consistently stronger associations in areas with higher oxidant gas concentrations for all three mortality outcomes (Fig. 1 and Supplemental Table 1). Similar trends were less apparent across tertiles of NO₂ or O₃ individually, particularly for O₃; however, risks of nonaccidental and respiratory mortality did increase across tertiles of NO₂ (Supplemental Table 2). The three-dimensional plots shown in Fig. 2 illustrate interactions across tertiles of PM_{2.5} and O_x for nonaccidental, cardiovascular, and respiratory mortality: for all three outcomes PM_{2.5}-mortality associations were strongest in the highest tertile of O_x.

Two Pollutant Models (PM_{2.5} and O_x). When two-pollutant models were examined including linear terms for PM_{2.5} and O_x, hazard ratios for PM_{2.5} decreased for all three mortality outcomes but remained elevated. The largest change occurred for the hazard ratio between PM_{2.5} and cardiovascular mortality which decreased from 1.107 (95% CI: 1.089, 1.127) in the single pollutant model to 1.024 (95% CI: 1.004, 1.044) in the two-pollutant model. The best fitting model for cardiovascular mortality included PM_{2.5}, O_x, and their interaction term (Table 4). For nonaccidental and respiratory mortality, model fit was similar between two pollutant models (i.e. containing PM_{2.5} and O_x) and models including both pollutants and their interaction term. The spatial distribution of PM_{2.5}*O_x is presented in Fig. 3 and highlights that the highest combined concentrations of PM_{2.5} and O_x occur in the most populated areas of Ontario and Quebec and along the southern border of Canada.

Joint Non-linear Models for PM_{2.5} and O_x. Effect modification by O_x was also apparent when we examined non-linear model forms for PM_{2.5}-mortality associations (Fig. 4). Specifically, the shapes of associations between O_x and θ (the parameter describing the magnitude of association between PM_{2.5} and mortality) were similar for all three causes of death (Fig. 4, panels a, c, and e) with threshold concentrations of 23.71 ppb, 25.08 ppb, and 25.13 ppb for cardiovascular, respiratory and nonaccidental mortality, respectively. The rate of change in θ per ppb of O_x above the threshold was greatest for cardiovascular mortality and similar for both non-accidental and respiratory mortality (λ values in the Supplemental Methods). Figure 4 (panels b, d, and e) illustrates non-linear concentration response relationships for PM_{2.5} and nonaccidental, cardiovascular, and respiratory mortality at O_x concentrations of 20.26 ppb (red solid line) and 37.6 ppb (blue solid line) which represent mean concentrations in the first and tenth deciles respectively of the O_x distribution. This Figure clearly illustrates considerable variations in PM_{2.5}-mortality associations at these two O_x concentrations.

Finally, Fig. 5 highlights areas of Canada with estimated O_x concentrations above 23 ppb. Based on the evidence above, reductions in O_x concentrations in these regions are expected to reduce the chronic health effects of PM_{2.5} even if mass concentrations remain unchanged.

Discussion

To our knowledge, this is the first large population-based cohort study to evaluate how oxidant gases may modify the chronic health risks of PM_{2.5}. In general, our findings suggest that oxidant gases act to enhance PM_{2.5}-mortality associations and that this effect modification occurs at O_x concentrations above approximately 23 ppb. This finding should be confirmed in future cohort studies as to our knowledge this study is the first to report such a relationship. If confirmed, these findings are important as they indicate that in some areas reductions in O_x concentrations may have the added benefit of reducing the public health impacts of PM_{2.5} even if mass concentrations remain unchanged.

While other studies have not examined the impact of oxidant gases on the chronic health effects of PM_{2.5}, we previously reported that O_x modified the association between short-term changes in ambient PM_{2.5} and the risk of emergency room visits for myocardial infarction⁸. In addition, others have reported associations between daily variations in O_x and mortality in London, England⁹. One possibility is that spatial variations in O_x concentrations are reasonable surrogates for the presence/absence of harmful air pollution mixtures and/or sources that are more relevant to health and thus PM_{2.5} in these regions tends to be more harmful. However, other biological mechanisms may also explain our observation of stronger PM_{2.5}-mortality associations in regions with higher O_x concentrations. First, ozone rapidly saturates the lung epithelial lining fluid where it degrades surfactants and depletes anti-oxidants; thus, oxidant gases may reduce our natural defense against reactive oxygen species generated in response to PM_{2.5} components including transition metals, polycyclic aromatic hydrocarbons, or quinones^{3,10}. In addition, ozone increases the permeability of the lung epithelium barrier^{4–7} and thus may facilitate the translocation of particles (or inflammatory proteins) from the lungs directly into the systemic circulation. Moreover, endogenous sources of oxidative stress may also play an important role as NO₂ has been shown to induce the release of reactive oxygen species from alveolar macrophages¹¹. Alternatively, photochemical aging of PM_{2.5} has been shown to increase the oxidative potential of particles themselves^{12,13}; therefore, this process may also contribute to our observation of stronger PM_{2.5}-mortality associations in regions with higher oxidant gas concentrations as photochemical oxidation would be greater in these areas.

Covariate	Persons	HR [†]	95% CI
All	2,448,500	—	—
Sex			
Male	1,185,500	—	—
Female	1,263,000	—	—
Age group (years)			
25 to 29	222,100	—	—
30 to 39	574,400	—	—
40 to 49	634,900	—	—
50 to 59	446,000	—	—
60 to 69	286,700	—	—
70 to 79	206,200	—	—
80 to 89	78,100	—	—
Visible minority status			
White or Aboriginal [§]	2,419,700	1.000	—
Visible minority	28,800	0.868	0.825–0.913
Marital status			
Single [§]	323,000	1.000	—
Common-law	294,700	0.788	0.769–0.807
Married	1,491,200	0.676	0.666–0.686
Separated	59,700	0.996	0.966–1.026
Divorced	140,700	1.006	0.985–1.028
Widowed	139,200	0.898	0.884–0.913
Educational attainment			
Not completed high school [§]	704,400	1.000	—
High school with/without trades certificate	887,600	0.803	0.795–0.810
Post-secondary non-university	473,600	0.670	0.660–0.680
University degree	382,900	0.551	0.542–0.561
Income adequacy quintile			
1st quintile - lowest [§]	373,600	1.000	—
2nd quintile	465,100	0.816	0.807–0.825
3rd quintile	509,900	0.711	0.702–0.720
4th quintile	537,400	0.633	0.625–0.642
5th quintile - highest	562,600	0.536	0.528–0.543
Labour force status			
Employed [§]	1,580,900	1.000	—
Unemployed	103,800	1.608	1.559–1.659
Not in labour force	763,800	1.944	1.917–1.971
Population Centre Size[§]			
Rural area [§]	641,800	1.000	—
Small population centre (1,000 to 29,999)	387,000	0.982	0.968–0.996
Medium population centre (30,000 to 99,999)	230,700	0.980	0.965–0.995
Large population centre (100,000 or more)	1,151,400	0.982	0.972–0.993
not assigned (dummy variable)	37,600	—	—
Airshed[‡]			
Western [§]	265,800	1.000	—
Prairie	288,600	1.083	1.062–1.104
West Central	164,900	1.115	1.091–1.139
East Central	1,376,300	1.035	1.021–1.049
South Atlantic	268,200	1.060	1.041–1.079
Northern	42,500	1.121	1.067–1.178
not assigned (dummy variable)	42,100	—	—
Ecological covariates - per 10% increase			
% unemployed	—	1.082	1.056–1.109
% not graduated high school	—	1.026	1.020–1.031
% low income	—	0.959	0.951–0.967
Population density - per IQR increase			
Continued			

Covariate	Persons	HR [†]	95% CI
Log population per km ² – Dissemination Area	—	0.996	0.991–1.000
Aboriginal status			
Not Aboriginal [§]	2,304,700	1.000	—
Aboriginal	143,700	1.704	1.673–1.736

Table 1. Descriptive statistics of the 2001 CanCHEC analytical sample, with Cox proportional hazard ratios among levels of each covariate. [§]Reference category. [†]Hazard ratios stratified by age (5 year categories) and sex. [‡]Based on first year of postal code data included or imputed for each respondent.

Pollutant	Percentile					Mean	Minimum	Maximum
	5 th	25 th	50 th	75 th	95 th			
PM _{2.5}	3.51	5.37	7.12	9.07	11.97	7.37	<1	20.00
O ₃	27.61	33.66	38.11	42.63	50.51	38.29	<1	60.46
NO ₂	3.36	6.44	10.31	15.10	24.52	11.47	<1	64.78
O _x	20.41	25.42	29.57	32.98	37.76	29.17	<1	49.30

Table 2. Descriptive statistics for PM_{2.5} (μg/m³), O₃ (ppb), NO₂ (ppb), and O_x (ppb) for all person-years in the cohort.

COD	Deaths	Air Pollutants			
		PM _{2.5}	O ₃	NO ₂	O _x
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
NAC	233,340	1.073 (1.062–1.083)	1.061 (1.051–1.070)	1.055 (1.046–1.064)	1.088 (1.077–1.099)
CV	77,000	1.107 (1.089–1.127)	1.170 (1.152–1.188)	1.045 (1.030–1.060)	1.198 (1.177–1.219)
RESP	21,100	1.089 (1.053–1.126)	1.043 (1.012–1.074)	1.091 (1.061–1.122)	1.086 (1.050–1.123)

Table 3. Hazard Ratios (95% CI) for relationships between nonaccidental, cardiovascular, and respiratory mortality and PM_{2.5}, NO₂, O₃, and O_x in CanCHEC 2001. COD, cause of death; NAC, non-accidental; CV, cardiovascular; RESP, respiratory. HRs reflect a 3.858 μg/m³ change in PM_{2.5}, an 8.111 ppb change in NO₂, a 10.503 ppb change in O₃, and an 8.760 ppb change in O_x.

One interesting finding in our investigation was that the rate of change in θ (the parameter describing the magnitude of association between PM_{2.5} and mortality) per ppb of O_x above the threshold was greater for cardiovascular mortality than respiratory mortality. One explanation for this finding may be that PM_{2.5} components and/or inflammatory mediators must first reach the systemic circulation from the lung in order to contribute to cardiovascular morbidity. If this process happens more quickly/efficiently at higher O_x concentrations (perhaps owing to increased lung permeability as noted above) this may explain the larger slope for θ in cardiovascular mortality. While we could not directly evaluate this question in the current study, future studies should aim to replicate this result as it may contribute to our understanding of how particulate air pollution influences cardiovascular morbidity/mortality.

This study had several important advantages including a large population-based sample of Canadians, exposure information for multiple air pollutants updated for residential mobility, detailed non-linear concentration-response modeling, and individual-level information on many important socio-economic factors. However, we cannot rule out potential confounding by unmeasured variables including smoking and obesity. In addition, as in all large scale epidemiological studies, exposure measurement error is a challenge and likely impacted our results. Specifically, the spatial scale of O₃ estimates was large and greater resolution is needed to refine or assessment of the spatial distribution of O_x (and PM_{2.5}*O_x) and associated health impacts. In general, measurement error for all air pollutants likely contained components of both Classical (i.e. grid-cell mean values distributed around true long-term ambient concentrations) and Berkson-type error (i.e. true individual-level exposures distributed around grid-cell mean values). Classical type error would tend to bias risk estimates toward the null whereas Berkson type error would tend to increase uncertainty in our estimates (i.e. wider confidence intervals). In either case, this error is not a likely explanation for our observed pattern of stronger PM_{2.5}-mortality associations in areas with higher O_x concentrations. Moreover, it is important to note that there is no clear consensus on the optimal spatial scale at which to evaluate long-term exposures to outdoor air pollution. Currently, the same spatial scale is applied to all cohort members but a more optimal approach may be to tailor the spatial scale of exposure assessment to match the size of individual-level activity spaces based on individual-level covariates such as age, sex, or socioeconomic status (e.g. older people may spend more time at home and thus a smaller spatial scale may be more appropriate for older cohort members). In some cases, larger spatial scales may be more appropriate if cohort members are highly mobile within their region and thus larger grid sizes are not necessarily a limitation. Nevertheless, more work is needed to refine air pollution exposure assessment in large population-based studies and our future work will aim to address several of these issues.

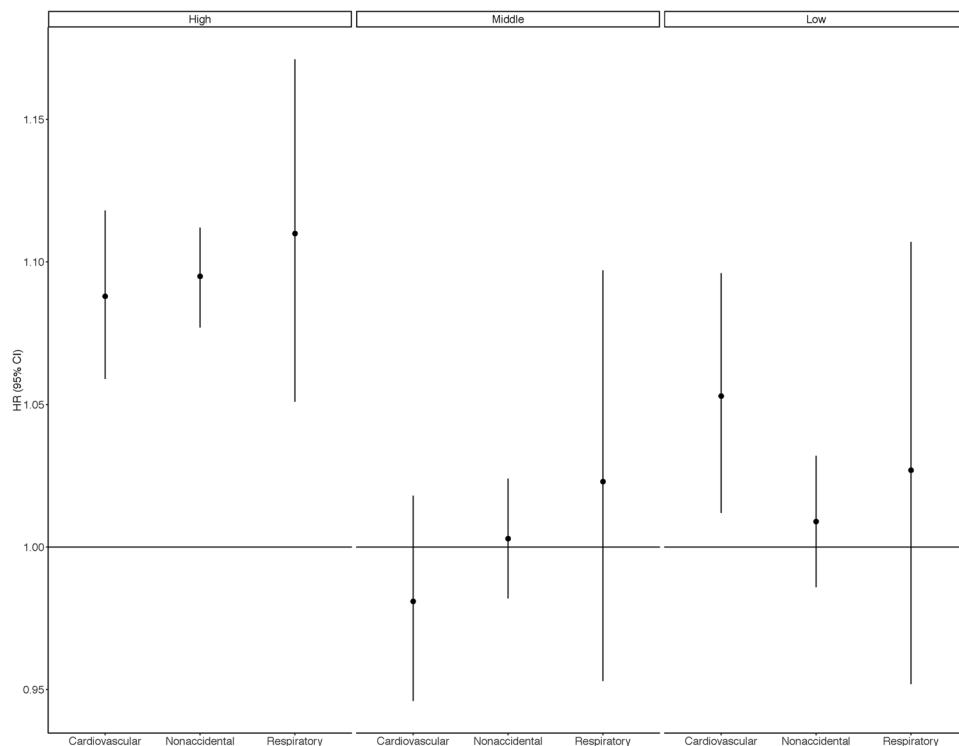


Figure 1. Hazard Ratios (95% CI) for relationships between $PM_{2.5}$ and mortality (nonaccidental, cardiovascular, and respiratory) across tertiles of O_3 in CanCHEC 2001. Hazard ratios reflect a $3.858 \mu\text{g}/\text{m}^3$ change in $PM_{2.5}$.

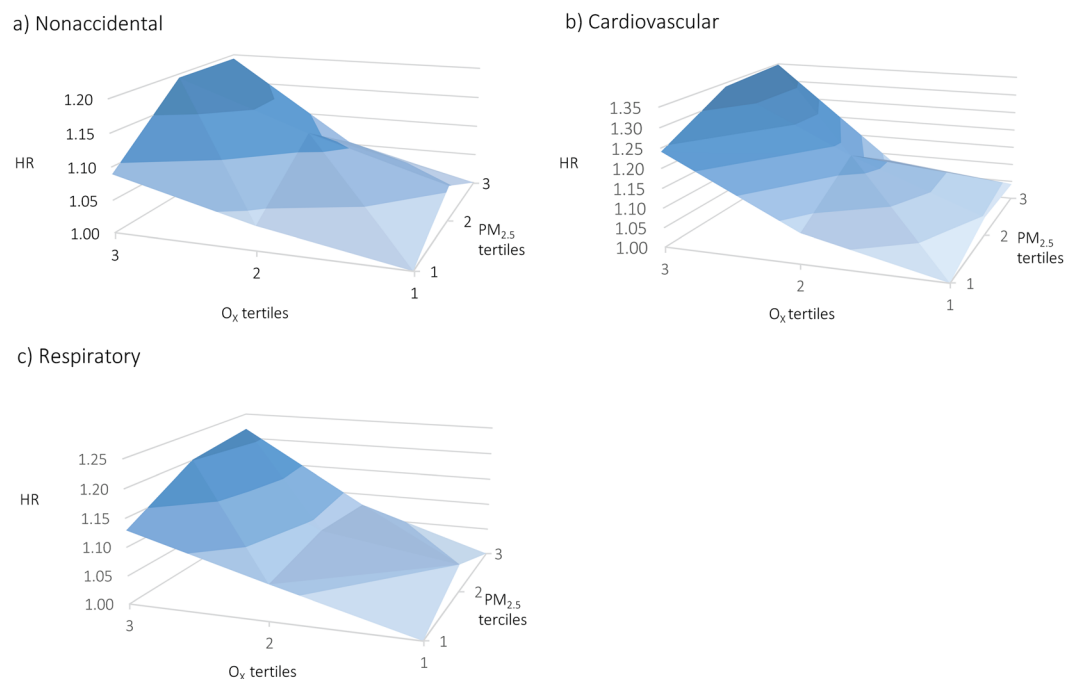


Figure 2. Three-dimensional plots of hazard ratios (HR) for (a) nonaccidental, (b) cardiovascular, and (c) respiratory mortality across tertiles of $PM_{2.5}$ and O_3 in CanCHEC 2001. Mean values across $PM_{2.5}$ tertiles are $4.58 \mu\text{g}/\text{m}^3$ (1), $7.18 \mu\text{g}/\text{m}^3$ (2), and $10.35 \mu\text{g}/\text{m}^3$ (3). Mean values across O_3 tertiles are 23.0 ppb (1), 29.2 (2), and 35.3 ppb (3).

In summary, the results of our cohort study suggest that oxidant gases may act to enhance the chronic health impacts of $PM_{2.5}$. If confirmed, our findings may provide additional flexibility for regulators/risk managers in reducing the overall public health impacts of $PM_{2.5}$. In particular, there may be important co-benefits to reducing

Model and Cause of Death	-2(LL)	Pollutant					
		O _x		PM _{2.5}		PM _{2.5} *O _x	
		HR	95% CI	HR	95% CI	HR	95% CI
PM_{2.5}							
Nonaccidental	3809180			1.073	1.062–1.083		
Cardiovascular	1227621			1.107	1.089–1.127		
Respiratory	330773			1.089	1.053–1.126		
PM_{2.5} + O_x							
Nonaccidental	3809055	1.067	1.055–1.080	1.041	1.029–1.052		
Cardiovascular	1227350	1.184	1.160–1.208	1.024	1.004–1.044		
Respiratory	330765	1.055	1.016–1.096	1.062	1.023–1.103		
PM_{2.5}*O_x							
Nonaccidental	3809092					1.054	1.047–1.060
Cardiovascular	1227481					1.094	1.082–1.105
Respiratory	330766					1.061	1.040–1.083
PM_{2.5} + PM_{2.5}*O_x							
Nonaccidental	3809075			0.947	0.923–0.972	1.087	1.070–1.104
Cardiovascular	1227388			0.800	0.764–0.837	1.242	1.208–1.278
Respiratory	330766			0.979	0.897–1.067	1.075	1.019–1.134
PM_{2.5} + O_x + PM_{2.5}*O_x							
Nonaccidental	3809054	1.056	1.032–1.081	1.019	0.978–1.061	1.026	0.978–1.077
Cardiovascular	1227346	1.141	1.096–1.188	0.954	0.889–1.024	1.091	1.004, 1.187
Respiratory	330765	1.039	0.962–1.122	1.030	0.900–1.179	1.039	0.885–1.220

Table 4. Potentiation of the relationship between PM_{2.5} and mortality (nonaccidental, cardiovascular and respiratory mortality) by O_x in CanCHEC 2001. Hazard ratios for O_x, PM_{2.5} and PM_{2.5}*O_x reflect changes of 8.76 ppb, 3.858 µg/m³ and 100 ppb*µg/m³ respectively.

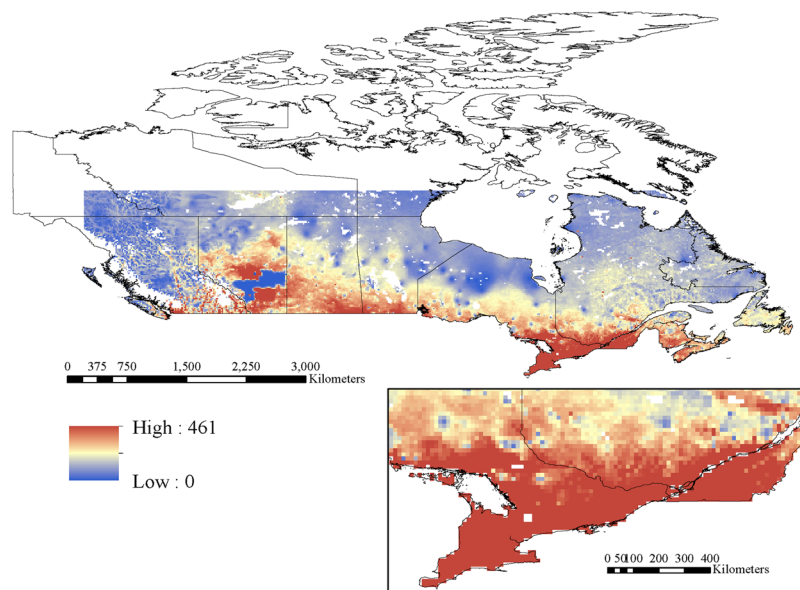


Figure 3. Spatial distribution of PM_{2.5}*O_x (ppb*µg/m³) across Canada. Map created in ArcGIS Desktop 10.0. ESRI, Redlands, CA (<http://desktop.arcgis.com/en/arcmap/>).

O_x as reductions in oxidant gas concentrations may also reduce the chronic health impacts of PM_{2.5} even if mass concentrations remain unchanged. The choice of which pollutant(s) to target in a given area will likely be situation-specific; however, knowledge of how oxidant gases and PM_{2.5} may interact to cause adverse health impacts could improve the efficiency of risk management activities and ultimately public health.

Methods

Study Population. This study uses the 2001 Canadian Census Health and Environment Cohort (CanCHEC) described in Pinault *et al.*¹⁴. Briefly, the 2001 Census long-form questionnaire was distributed to approximately 20% of Canadian households including 4,500,200 Census respondents aged 19 years or older who did not reside

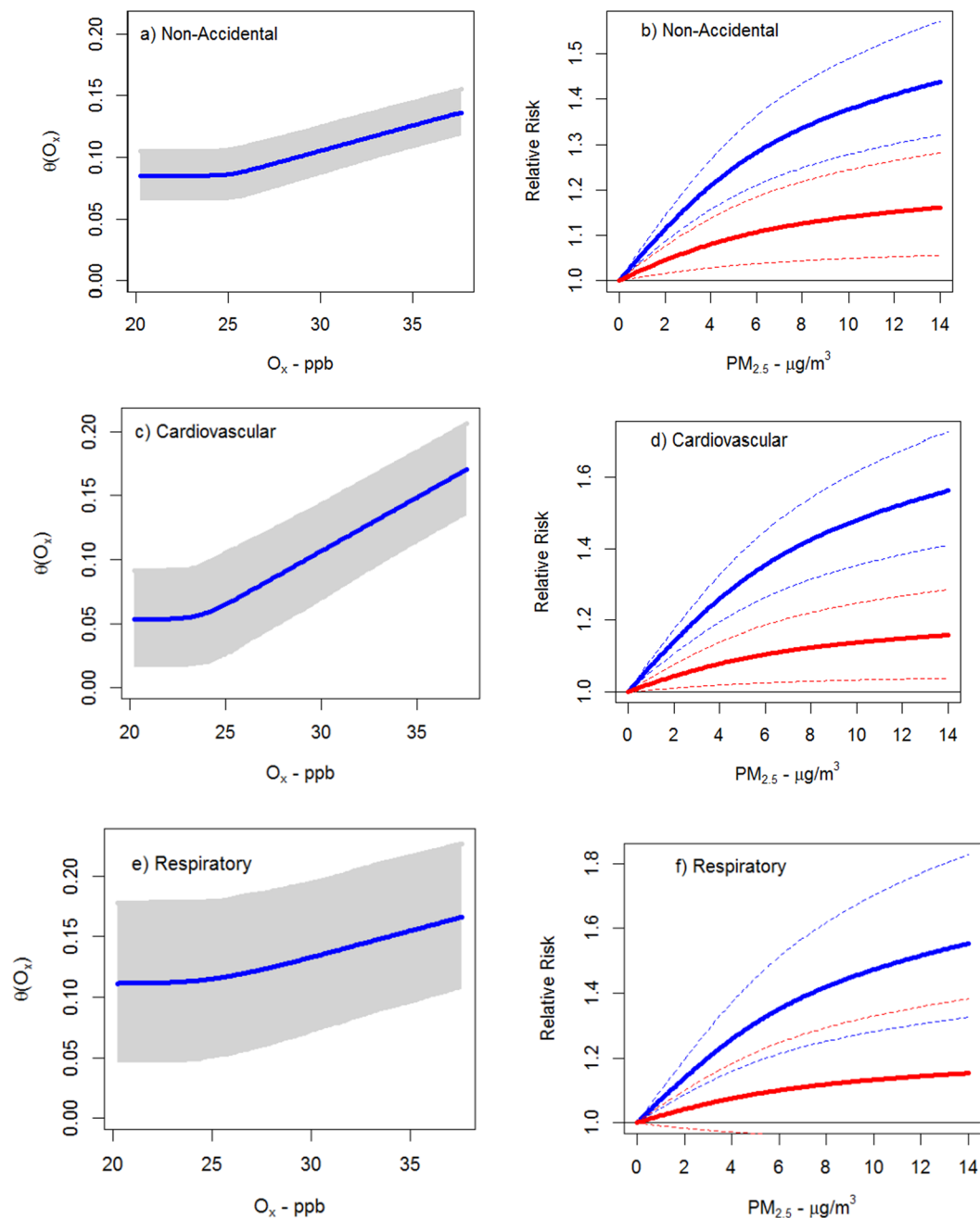


Figure 4. Predicted values (solid blue line) of $\hat{\theta}(O_x) = \hat{\eta} + \hat{\lambda}(O_x - \omega)_+$ by cause of death with uncertainty bounds (shaped gray area) (panels a, c, and e). Predicted values of $R(PM_{2.5}) = (1 + PM_{2.5})^{\hat{\theta}(O_x)/(1 + \exp(-z/2))}$ for $O_x = 37.60$ ppb (solid blue line) and $O_x = 20.26$ ppb (solid red line) with uncertainty intervals (dashed lines) (panels b, d, f).

in institutions and who lived in Canada¹⁵. Of these, 78.6% ($n = 3,537,500$) were linked to income tax files to obtain annual postal code histories and Social Insurance Numbers through standard deterministic and probabilistic linkage techniques¹⁶. These subjects were then deterministically linked to the Amalgamated Mortality Database using Social Insurance Numbers. All deaths that occurred between census day (May 15, 2001) and December 31, 2011 were eligible for linkage.

Respondents who were not assigned air pollution estimates due to living outside the boundaries of air pollution models were excluded ($n = 86,100$) as were those less than 25 years of age or older than 90 years ($n = 319,900$ additional persons excluded). All immigrants were also excluded from the cohort ($n = 683,100$) since their previous air pollution exposures were unknown. The final analytical sample was 2,448,500 respondents: sample sizes are rounded to the nearest hundred for confidentiality.

Postal code histories obtained from tax records were used to geocode respondent addresses. Statistics Canada's Postal Code Conversion File plus (PCCF+) v.6c uses a population-weighted random allocation algorithm to

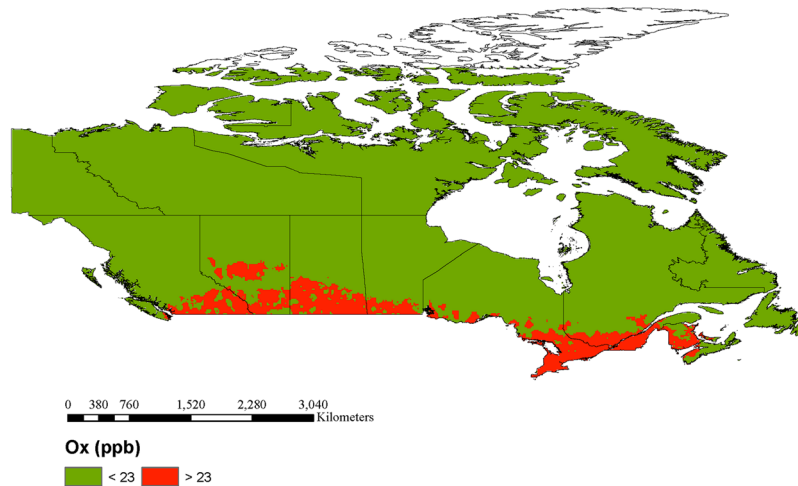


Figure 5. Regions of Canada with estimated O_x concentrations above 23.0 ppb. Reductions in O_x concentrations in these areas are expected to decrease the chronic health risks of $PM_{2.5}$ even if mass concentrations remain unchanged. Map created in ArcGIS Desktop 10.0. ESRI, Redlands, CA (<http://desktop.arcgis.com/en/arcmap/>).

assign geographic coordinates to postal codes based on centroids of different scales of Census geography¹⁷. The gaps in postal code reporting (approximately 18% of all person-years) were imputed using a probabilistic imputation method developed at Statistics Canada, which assigned postal code common characters from postal codes provided before and after the gap in reporting¹⁸. The method included a non-null probability that missing postal codes would be different from adjacent years, and the probability of non-matches increased with increasing gap length. In cases where postal codes were not imputed using any common characters, the national mean exposure estimate was assigned. In a validation exercise with the 1991 CanCHEC, when 5% of postal codes were randomly deleted and then imputed using the program, 4.2% of imputed postal codes had an absolute $PM_{2.5}$ difference greater than $0.1 \mu\text{g}/\text{m}^3$ ¹⁸. In general, 2001 CanCHEC members were more likely to be married or common-law, have higher income or higher educational attainment, or be employed than were the general Canadian population¹⁴.

Exposure Assessment. Cohort members were assigned air pollution exposure estimates for $PM_{2.5}$, NO_2 , and O_3 using models that have been previously described. Specifically, $PM_{2.5}$ exposures were derived from a surface model that combines information for total column aerosol optical depth retrievals from the Moderate Resolution Imaging Spectroradiometer (MODIS) with near-surface $PM_{2.5}$ emissions estimated from the GEOS-Chem chemical transport model¹⁹. Yearly (2012 to 2014) average surface layers of $PM_{2.5}$ (at 1 km^2 resolution) were obtained by applying geographically weighted regression, and extended back in time to 1998 by applying inter-annual variation from a published model²⁰. Within North America, mean $PM_{2.5}$ estimates were strongly correlated with ground level measurements ($R^2 = 0.82$, slope = 0.97, $n = 1440$)¹⁹. Estimates of $PM_{2.5}$ that were greater than $20 \mu\text{g}/\text{m}^3$ were excluded from the analysis because they likely represented inaccurate satellite retrievals.

Outdoor NO_2 concentrations were estimated using the 2006 annual mean from a national land use regression model that used National Air Pollution Surveillance (NAPS) fixed-site monitoring data combined with satellite NO_2 estimates, road length within 10 km, industrial land use areas within various buffers, and mean summer rainfall²¹. Ground-level NO_2 estimates were derived using GEOS-Chem from satellite tropospheric NO_2 columns²². During validation, the model explained 73% of the variance in 2006 NAPS estimates. Local variation in NO_2 was captured by applying kernel density measures of highways and major roads as a multiplier to the model²¹.

A surface for average daily 8-hr maximum O_3 concentration was generated for the months of May to October for the period of 2002 to 2009 using an air pollution-specific interpolation technique to generate a 21 km^2 grid^{2,23}. This method incorporates modeled O_3 from the Canadian Hemispheric Regional Ozone and NO_x system (CHRONOS) air quality forecast model²⁴ with observations from Canada and the United States.

All NO_2 and ozone data were year-adjusted using ground-based time-series measurements from 24 Census Divisions (CD)s between 1981 and 2012. The time series for NO_2 and O_3 were derived from NAPS daily average concentrations (if at least 18 hourly concentrations were recorded in a day), and averaged for CD's with more than one monitoring station²⁵. Missing time-series data were imputed using an interpolation algorithm that combines classical prediction techniques and the phase-and frequency-fitting tools via the multi-taper method using the R package *tsinterp*²⁶. For each CD time-series, a cubic spline was fitted to model the association between year and air pollutant concentration. Then, the ratio between the year of the original modeled data (i.e., NO_2 : 2006, O_3 : mean of 2002 to 2009) and all years of follow-up was determined. For each year of follow-up, residence locations for cohort members were matched to the closest CD in Geographic Information Systems (ArcGIS v.10, ESRI 2010), and the corresponding time adjustment ratio was used to adjust data for annual differences in concentration. All air pollution exposures were assigned using 3-year moving averages with a 1-year lag time (and updated for residential mobility).

Finally, the combined oxidant capacity (O_x) of O_3 and NO_2 at each residential location was calculated as a weighted average with weights equivalent to their respective redox potentials (i.e. $O_x = [(1.07 \times NO_2) + (2.075 \times O_3)]/3.145$)²⁷.

Statistical Analyses. Standard Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) describing the relationship between outdoor air pollutants and nonaccidental (ICD-10: A to R), cardiovascular (ICD-10: I10-69 and E10-E14 (diabetes)), and respiratory mortality (ICD-10: J00-J99). All models were stratified by age (5-year categories), sex, airshed, and population centre size, and adjusted for individual-level covariates including visible minority status, Aboriginal status, marital status, educational attainment, income quintile, and labour force status. In addition, several neighbourhood-level covariates were included in the models including percent unemployed (aged 25 and older), percent not graduated from high school (aged 25 and older), and percent low income status within census divisions as well as population density (per km²) within dissemination areas (Table 1). All hazard ratios for individual pollutants are expressed for intervals equivalent to the difference between the mean and the 5th percentile of each pollutant. Hazard ratios for the product of $PM_{2.5}$ and O_x are expressed per 100 ppb* $\mu g/m^3$.

A series of models were examined to evaluate how oxidant gases may modify the relationship between $PM_{2.5}$ and mortality. First, single pollutant models were examined using linear terms for $PM_{2.5}$, NO_2 , O_3 , and O_x (as defined above). Hazard ratios for $PM_{2.5}$ were then calculated across tertiles of O_x to evaluate trends in $PM_{2.5}$ -mortality associations at increasing concentrations of oxidant gases; the entire range of $PM_{2.5}$ concentrations (i.e. 1–20 $\mu g/m^3$) was available within each tertile of O_x . Three-dimensional plots were also examined for hazard ratios across tertiles of O_x and $PM_{2.5}$.

Next, two pollutant models including both $PM_{2.5}$ and O_x were examined to evaluate potential confounding by O_x in $PM_{2.5}$ -mortality associations followed by: 1) models including only the product of $PM_{2.5}$ and O_x (i.e. $PM_{2.5} * O_x$); 2) models including $PM_{2.5}$ and the product of $PM_{2.5}$ and O_x (i.e. $PM_{2.5} + PM_{2.5} * O_x$); and 3) models including $PM_{2.5}$, O_x , and product of $PM_{2.5}$ and O_x (i.e. $PM_{2.5} + O_x + PM_{2.5} * O_x$). Our primary aim in evaluating this series of models was to examine how O_x may modify the relationship between $PM_{2.5}$ and mortality using linear terms for individual pollutants both excluding and including the main effect of O_x . Following the above analyses, we considered non-linear model forms to characterize potential effect modification due to O_x on $PM_{2.5}$ -mortality associations as outlined below.

The traditional relative risk function used to relate $PM_{2.5}$ concentrations to mortality is: $R(PM_{2.5}) = \exp\{\theta \times PM_{2.5}\}$ with θ representing the logarithm of the relative risk for a unit change in $PM_{2.5}$, assuming a linear relationship between $PM_{2.5}$ and the logarithm of the relative risk. This model has been extended to include non-linear model specifications of the form: $R(PM_{2.5}) = \exp\{\theta \times T(PM_{2.5})\}$, where $T(PM_{2.5})$ is a monotonic transformation of $PM_{2.5}$ ^{28,29}. Here, θ represents the logarithm of the relative risk for a unit change in $T(PM_{2.5})$. Setting $T(PM_{2.5}) = \log(\mathcal{J}(PM_{2.5}))/1 + \exp(-(PM_{2.5} - \mu)/\pi)$, where $\mathcal{J}(z) = e^z$ or $\mathcal{J}(z) = 1 + z$, specifies a family of shapes taking supra-linear, near-linear, sub-linear and sigmoidal forms depending on (\mathcal{J}, μ, π) .

In this study, we examined how mortality risks due to $PM_{2.5}$ exposures may be affected by co-occurring exposure to O_x . To do this, we introduced the notion that the parameter θ can vary with concentrations of O_x by defining a joint relative risk function of the form: $R(PM_{2.5}, O_x) = \exp\{\theta(O_x) \times T(PM_{2.5})\}$. We additionally postulated that there exists a concentration of O_x , ω , below which, O_x does not modify the risk of death due to $PM_{2.5}$ exposure and above that concentration there exists a linear association. That is: $\theta(O_x) = \eta + \lambda \times (O_x - \omega)_+$, such that $(O_x - \omega)_+ = 0$ if $O_x < \omega$ and $(O_x - \omega)_+ = (O_x - \omega)$ if $O_x \geq \omega$, for concentration ω . It is important to note that this model does not directly evaluate the impact of O_x on mortality; rather, it redistributes $PM_{2.5}$ risk according to concentrations of O_x . Methods to estimate the unknown parameters and their uncertainty are presented in the Supplemental Material.

All statistical analyses were conducted using R version 3.2.4 and SAS version 9.3. Map Figures were created in ArcGIS 10.0 (ESRI, 2010). NO_2 and O_3 surfaces were created using interpolation (i.e. inverse distance weighted) from nationally representative NO_2 and O_3 point estimates, and raster algebra was used to calculate O_x and the product of O_x and $PM_{2.5}$ using published $PM_{2.5}$ surfaces¹⁹. All data are available through the Statistics Canada Research Data Centers located across Canada conditional on the necessary institutional approvals from Statistics Canada including security screening.

Institutional Approvals. The Canadian Census Health and Environment Cohort (CanCHEC) was approved by the Statistics Canada Policy Committee (reference number 012-2001) after consultation with the Statistics Canada Confidentiality and Legislation Committee, Data Access and Control Services Division, and the Federal Privacy Commissioner. This approval is equivalent to that of standard research ethics boards.

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Author Contributions

S.W. was the lead author and wrote the main manuscript text and prepared Fig. 1. L.P. and R.B. conducted all statistical analyses and contributed to writing the methods section of the manuscript. L.P. prepared Figs 2, 3, and 5 and Supplemental Figures S1–S4. R.B. prepared Fig. 4.

Additional Information

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