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Association of Sulfur, Transition Metals, and the Oxidative Potential of Outdoor $PM_{2.5}$ with Acute Cardiovascular Events: A Case-Crossover Study of Canadian Adults

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Background: We do not currently understand how spatiotemporal variations in the composition of fine particulate air pollution [fine particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$)] affects population health risks. However, recent evidence suggests that joint concentrations of transition metals and sulfate may influence the oxidative potential (OP) of $PM_{2.5}$ and associated health impacts.

Objectives: The purpose of the study was to evaluate how *combinations* of transition metals/OP and sulfur content in outdoor $PM_{2.5}$ influence associations with acute cardiovascular events.

Methods: We conducted a national case-crossover study of outdoor $PM_{2.5}$ and acute cardiovascular events in Canada between 2016 and 2017 (93,344 adult cases). Monthly mean transition metal and sulfur (S) concentrations in $PM_{2.5}$ were determined prospectively along with estimates of OP using acellular assays for glutathione (OP^{GSH}), ascorbate (OP^{AA}), and dithiothreitol depletion (OP^{DTT}). Conditional logistic regression models were used to estimate odds ratios (OR) [95% confidence intervals (CI)] for $PM_{2.5}$ across strata of transition metals/OP and sulfur.

Results: Among men, the magnitudes of observed associations were strongest when *both* transition metal and sulfur content were elevated. For example, an OR of 1.078 (95% CI: 1.049, 1.108) (per 10 $\mu g/m^3$) was observed for cardiovascular events in men when both copper and S were above the median, whereas a weaker association was observed when both elements were below median values (OR = 1.019, 95% CI: 1.007, 1.031). A similar pattern was observed for OP metrics. $PM_{2.5}$ was not associated with acute cardiovascular events in women.

Discussion: The *combined* transition metal and sulfur content of outdoor $PM_{2.5}$ influences the strength of association with acute cardiovascular events in men. Regions with elevated concentrations of *both* sulfur and transition metals in $PM_{2.5}$ should be examined as priority areas for regulatory interventions. https://doi.org/10.1289/EHP9449

Introduction

Numerous epidemiological studies have documented the acute cardio-respiratory health impacts of outdoor fine particulate air pollution [fine particulate matter with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$)] (Achilleos et al. 2017; Atkinson et al. 2014; Yang et al. 2019). To date, most studies have relied on $PM_{2.5}$ mass concentrations as the primary exposure of interest without considering spatial or temporal differences in particle composition that may affect overall health risks. Because $PM_{2.5}$ is a complex and dynamic mixture of organic and inorganic components, treating all particle mass concentrations as equally harmful has clear limitations, and doing so may contribute to spatial heterogeneity in estimated health risks (Liu et al. 2019). Recently, an increasing number of studies have incorporated measures of particle oxidative potential (OP) to complement traditional mass-based measurements because oxidative stress is an important mechanism contributing to air pollution health effects (Bates et al. 2019; Rao et al. 2018). Moreover, recent analysis of atmospheric particles suggests that soluble metals and OP peak at the intersection of sulfate and transition metal concentrations in $PM_{2.5}$ (Fang et al. 2017). Therefore, if soluble metals and OP are important determinants of the magnitude of health risks associated with $PM_{2.5}$, it may be necessary to consider both of these components *simultaneously* in epidemiological analyses.

In Canada, we previously reported evidence of effect modification by particle OP in a panel study of personal $PM_{2.5}$ exposures and airway inflammation in children who have asthma (Maikawa et al. 2016), in a cohort study of outdoor $PM_{2.5}$ and preterm birth (Lavigne et al. 2018), and in case-crossover studies of daily $PM_{2.5}$ and emergency room visits for myocardial infarction (Weichenthal et al. 2016a) and asthma (Weichenthal et al. 2016b). In all of these studies, the short-term health impacts of $PM_{2.5}$ were greater when glutathione-related oxidative potential (OP^{GSH}) was higher as determined using a cell-free assay based on a synthetic respiratory tract lining fluid. However, other studies have not found evidence of effect modification by OP in evaluating the acute health impacts of $PM_{2.5}$ (see review by Atkinson et al. 2016). To our knowledge no epidemiological studies to date have examined how the acute cardiovascular health risks of $PM_{2.5}$ may vary based on *combinations* of transition metal and sulfur content or how spatiotemporal variations in combinations of these components may be related to particle OP. To address this need, we conducted a national-scale case-crossover study of outdoor $PM_{2.5}$ mass concentrations and acute cardiovascular events including prospective monthly measurements of sulfur (as a marker for sulfate and indirectly metal solubility) and transition metals in $PM_{2.5}$ as well as three different metrics of $PM_{2.5}$ OP (as monthly means).

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Methods

Study Design

A time-stratified case-crossover design (Janes et al. 2005) was used to estimate associations between short-term changes in outdoor $PM_{2.5}$ mass concentrations and hospital admissions for cardiovascular outcomes across strata of OP, mass proportions (percent) of transition metals [i.e., copper (Cu), iron (Fe), nickel (Ni), manganese (Mn), zinc (Zn)], and S (sulfur) in monthly $PM_{2.5}$ samples (described below). The time-stratified case-crossover design selects reference periods matched on the same day of the week, month, and year as event days (i.e., if a case occurs on the first Friday of June 2021, the references days are all other Fridays in June 2021). Our analysis included the following 34 locations across Canada (Figure 1) (all cities had a single monitor unless otherwise indicated): Red Deer, Edmonton (two sites), St. Albert, Regina, Hamilton, Victoria, Ottawa (two sites), Montreal, Winnipeg, St. John's, Courtenay, Windsor, Duncan, Saskatoon, Quebec City, Kelowna, Prince George, Kamloops, London, Mt. Pearl, Prince Albert, Nanaimo, Fort Mackay, Whitehorse, Swift Current, Fort McMurray, Brandon, Calgary, Yellowknife, Athabasca Valley, Quesnel, Halifax, Saint John, and Fredericton.

All adult cases (ages 18–100 y) of acute cardiovascular events were identified between 1 June 2016 and 31 December 2017 to overlap with the timing of monthly OP/component measurements. Specifically, hospital admissions for cardiovascular outcomes [*International Classification of Diseases (ICD), 10th revision*, Code I00-I99] were identified using the Discharge Abstract Database (DAD) maintained by the Canadian Institute for Health Information (CIHI) along with information on age, sex, and residential postal code. The DAD captures hospital admissions across Canada with the exception of Quebec (Gibson et al. 2008). Quebec data were obtained from the Quebec Ministry of Health and Social Services through MED-ÉCHO (Ministère de la Santé et des Services Sociaux 2021). Cases were included in case-crossover analyses if at the time of admission their residential 6-digit postal code (about the size of a city block face) was within 5 km of a monitoring site for daily $PM_{2.5}$ (which in most cases was the same location where OP and $PM_{2.5}$ components were measured). Fatal cases were included in the analysis, but readmissions were excluded (i.e., if the same person was admitted twice, only the first visit was included). Ethics approval for this study was granted through data sharing agreement between Health Canada and CIHI.

Monthly $PM_{2.5}$ Sample Collection

Integrated $PM_{2.5}$ samples were collected on Teflon™ filters at each study location for 2 wk each month using cascade impactors operating at a flow rate of 5 L per minute. In most cities, monthly $PM_{2.5}$ samplers were located at provincial monitoring sites (i.e., the same locations that provided daily $PM_{2.5}$ data) except for Ottawa (2.1 km from the location of daily $PM_{2.5}$ measurements) and Montreal (2.7 km from the location of daily $PM_{2.5}$ measurements) where OP/component measurements were collected outside private residences (located at ground level in Ottawa and approximately 6 meters off the ground in Montreal). Following gravimetric analyses, monthly $PM_{2.5}$ filters were analyzed for sulfur and transition metal content using X-ray fluorescence (U. S. Environmental Protection Agency Method IO-3.3) and oxidative potential as described below. The following transition metals were selected for inclusion in our analyses based on previous evidence suggesting an association with particle OP: Cu, Fe, Zn, Ni, and Mn (Charrier and Anastasio 2012; Fang et al. 2017; Gao et al. 2020; Verma et al. 2014). It is important to note that although analyses were conducted across strata of specific metals, we cannot conclusively attribute the results to specific transition metals, because trace metals tended to be highly correlated. If more than one sample was collected from a site in a given month, samples were averaged to obtain a single monthly estimate.

OP Measurements

Monthly $PM_{2.5}$ samples were extracted into high-performance liquid chromatography high-performance liquid chromatography (HPLC) grade methanol by vortexing at 1,800 rpm for 20 min and sonicating for 10 min. Decanted methanol was evaporated under a gentle flow of nitrogen. PM samples were resuspended in ultrapure water containing 5% HPLC methanol to a final storage concentration of 200 μg PM/mL. Resuspended $PM_{2.5}$ samples were analyzed in triplicate using three OP metrics: the ascorbate (AA), glutathione (GSH), and dithiothreitol (DTT) assays. Ascorbate and glutathione oxidative potential (OP^{AA} and OP^{GSH}) were assessed using the acellular respiratory tract lining fluid (RTLF) OP assay (Maikawa et al. 2016; Weichenthal et al. 2019). Briefly, $PM_{2.5}$

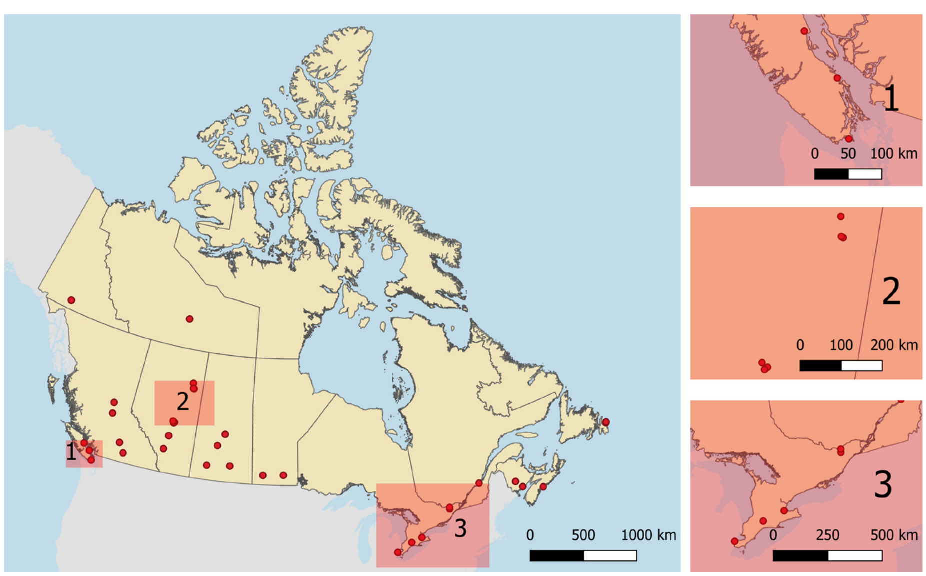

Figure 1. Locations of monitoring sites for $PM_{2.5}$ components and oxidative potential across Canada (2016–2017).

samples were incubated at a concentration of 75 $\mu g/mL$ in a 96-well plate for 4 h at 37°C with synthetic respiratory tract lining fluid (RTLF) containing 200 μM of each AA, GSH, and uric acid in an ultraviolet-visible plate reader (SpectraMax 190; Molecular Devices) alongside positive controls (0.5 μM $Cu(NO_3)_2$, 0.02% H_2O_2) and blanks. Ascorbate depletion was calculated over the 4-h incubation period, and GSH depletion was measured using the glutathione-reductase enzyme recycling assay (Baker et al. 1990; Godri et al. 2010; Griffith 1980; Mudway et al. 2004).

Dithiothreitol OP (OP^{DTT}) was assessed using an adapted version of the DTT assay (Cho et al. 2005). Briefly, resuspended $PM_{2.5}$ samples were incubated with 100 μM DTT in a 96-well plate alongside positive controls [0.5 μM $Cu(NO_3)_2$], blanks, and DTT standards (containing 0–100 μM DTT) for 35 min at 37°C, with constant shaking. After 5, 15, 25, and 35 min, the remaining DTT was measured by adding 1.0 mM 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB) to each well and measuring absorbance at 412 nm. Samples were initially analyzed at a concentration of 50 $\mu g/mL$; however, if DTT depletion exceeded 25% after 35 min, the sample was reanalyzed at a lower concentration. All OP values are expressed in units of picomoles per minute per microgram; values below detection were replaced with half the limit of detection.

Daily Air Pollution Data

Daily mean outdoor concentrations of $PM_{2.5}$, NO_2 and O_3 were obtained from fixed-site monitoring stations operated by the National Air Pollution Surveillance network maintained by Environment and Climate Change Canada. O_x was calculated as a weighted average of NO_2 and O_3 using redox potentials as the weights {i.e., $O_x = [(1.07\ V \times NO_2) + (2.075\ V \times O_3)]/3.145\ V$, where V refers to volts; Weichenthal et al. 2016a}. The redox-weighted measure accounts for the fact that O_3 is a stronger oxidant than NO_2. Case and control periods were assigned outdoor $PM_{2.5}$ concentrations based on these fixed-site monitoring data. Daily mean temperature and relative humidity data were also provided by Environment and Climate Change Canada using mean 24-h values from the closest weather station.

Statistical Analyses

Conditional logistic regression models were used to estimate associations [odds ratios (OR) and 95% confidence intervals (CI)] between lag-0 (i.e., same day) concentrations (including the case day) and hospital admissions for cardiovascular outcomes adjusting for continuous measures of lag-0 mean temperature and O_x concentrations. This lag period was selected based on past analyses of the acute cardiovascular health impacts of $PM_{2.5}$ that suggested that same-day exposures were most strongly associated with the outcome (Weichenthal et al. 2016a). Natural cubic splines with 3 knots were also examined for temperature and O_x but gave results similar to those of models including linear terms (Table S1), likely owing to the restricted range of values across within-subject comparisons (i.e., the exposure variance of interest is case-crossover studies relates to the distribution of pollutant *differences* between case and control periods, which is generally much less than day-to-day variations across the study period) (Künzli and Schindler 2005). Relative humidity was not correlated with outdoor $PM_{2.5}$ ($r = 0.1$) and was not included as a confounder in the analyses. Lag-0 O_x concentrations were not correlated with lag-0 $PM_{2.5}$ concentrations ($r = -0.055$) but were included *a priori* as a covariate in our models because we previously observed an association between daily O_x and acute myocardial infarction (Weichenthal et al. 2016a). Lag-0 O_x concentrations were not correlated with monthly average OP ($-0.016 < r < 0.047$) or mass proportions of transition metals (i.e., Cu, Fe, Zn, Ni, Mn) in $PM_{2.5}$ ($0.01 < r < 0.11$). Other time-varying confounding factors were not examined in the models. Models for 3-d mean $PM_{2.5}$ concentrations were evaluated, but results were similar (but slightly attenuated) to those for lag-0, and thus we focus only on results for lag-0 concentrations (Table S2). A cluster variance estimator was used to account for potential within-city clustering of observations.

All analyses were conducted separately for men and women, because initial analyses looking only at $PM_{2.5}$ mass concentrations suggested stronger associations among men (Table S2; interaction p-value for lag-0 $PM_{2.5} = 0.027$). The interaction between $PM_{2.5}$ and sex was evaluated by including a product term in conditional logistic regression models; a p-value less than 0.05 was considered statistically significant. Among men and women, we also examined models stratified by age (i.e., above/below the median age of 70 y) but did not perform formal tests for effect modification by age.

Stratified analyses were conducted for lag-0 $PM_{2.5}$ across strata defined by monthly measurements of OP^{GSH}, OP^{AA}, OP^{DTT}, metals, and S in $PM_{2.5}$. To maximize the number of cases in each cell (between approximately 10,000–18,000 for men and 7,000–12,000 for women), strata for transition metals, OP, and S were based on median values in monthly $PM_{2.5}$ samples [this provided a sample size 2–3 times greater than a recent case-crossover study of the acute cardiovascular health impacts of $PM_{2.5}$ in Canada at similar concentrations (Weichenthal et al. 2017)]. These analyses provided estimates of associations between lag-0 $PM_{2.5}$ concentrations and acute cardiovascular outcomes across various combinations of monthly average S and metals/OP. Using these models, we also calculated p-values for interactions between lag-0 $PM_{2.5}$ and monthly S (by including an interaction term between lag-0 $PM_{2.5}$ and an indicator variable for S) separately for strata defined by median metals/OP concentrations. This calculation was done to determine whether the pattern of effect modification by S also depended on metal/OP concentrations. A third strata for S was also evaluated (≥90th percentile, including between 1,200 and 3,500 cases) to examine patterns on the upper end of the S distribution but was not included in formal tests of interactions. Similarly, we calculated p-values for interactions between lag-0 $PM_{2.5}$ and monthly metals/OP (by including an interaction term between lag-0 $PM_{2.5}$ and indicator variables for metals/OP) separately for strata defined by median S concentrations. This calculation was done to determine whether the pattern of effect modification by metals/OP also depended on S concentrations. Finally, three-way interactions were also examined including interaction terms between lag-0 $PM_{2.5}$ and indicators variables (above/below monthly median) for metals/OP (separately) and S. All ORs reflect a 10 $\mu g/m^3$ change in outdoor $PM_{2.5}$ to facilitate comparisons with other studies of outdoor $PM_{2.5}$. All statistical analyses were conducted using R (version 4.0; R Development Core Team). Three-dimensional plots were generated using generalized additive models in the *mgcv* package in R with three knots (for each dependent variable) (Wood 2021).

Results

In total, 93,344 cases of acute cardiovascular events were included in the analysis; 3,765 eligible cases (3.9%) were excluded because of missing data for daily $PM_{2.5}$. Cases were predominantly male (54,338 men and 39,006 women), with a mean age of 70 y [standard deviation (SD) = 15 y]. Daily mean $PM_{2.5}$ concentrations were low (mean = 7.25 $\mu g/m^3$; SD = 6.68), but monthly OP, transition metal, and S concentrations varied substantially across the study period (Table 1; descriptive data for element mass

Table 1. Descriptive statistics for daily data used in case-crossover analyses and monthly estimates of $PM_{2.5}$ (micrograms per cubic meter), oxidative potential [glutathione (OP^{GSH}), ascorbate (OP^{AA}), and dithiothreitol-related oxidative potential (OP^{DTT})], and $PM_{2.5}$ components (Canada, 2016–2017).

Pollutant/component	Mean	SD	5th	25th	50th	75th	95th
Daily air pollutants and temperature							
$PM_{2.5}$ ($\mu g/m^3$)	7.25	6.86	1.79	3.83	5.87	8.83	16.5
O_3 (ppb)	23.1	8.37	9.70	17.4	22.8	28.9	36.9
NO_2 (ppb)	8.54	5.85	2.00	4.46	7.17	11.0	20.0
O_x (ppb)	18.2	5.03	10.3	14.7	17.9	21.6	26.6
Temperature (°C)	7.68	11.2	−13.4	0.0404	9.14	16.9	22.4
Monthly average components							
$PM_{2.5}$ ($\mu g/m^3$)	7.67	5.47	3.27	5.17	6.82	9.08	14.3
OP (pmol/min/μg)							
OP^{GSH}	3.45	1.98	1.03	2.09	3.09	4.35	7.62
OP^{AA}	2.91	0.91	1.46	2.29	2.79	3.50	4.67
OP^{DTT}	11.9	7.46	2.12	6.05	10.2	16.6	26.5
Elements (ng/m^3)							
S	261	139	97.6	162	242	314	520
Cu	3.18	3.08	0.501	1.06	1.95	4.28	9.00
Fe	93.7	61.1	20.6	43.3	83.4	130	205
Ni	0.460	0.81	0.0554	0.121	0.207	0.419	2.12
Mn	3.26	2.67	0.555	1.34	2.82	4.19	7.52
Zn	12.4	13.3	1.99	3.93	6.83	15.6	39.4

Note: Cu, copper; Fe, iron; Mn, manganese; Ni, nickel; OP, oxidative potential; OP^{AA}, ascorbate; OP^{DTT}, dithiothreitol; OP^{GSH}, glutathione; ppb, parts per billion; S, sulfur; SD, standard deviation; Zn, zinc.

proportions are shown in Table S3). Distributions of monthly $PM_{2.5}$ components (i.e., transition metals and S) were based on 685 samples, whereas 636 samples were available for OP^{GSH}, 637 for OP^{AA}, and 634 for OP^{DTT}.

As shown in Figure 2, correlations between metals and OP were stronger when S concentrations were higher. For example, when S was below the median, OP^{GSH} was only weakly correlated with Fe ($r = -0.01$), Cu ($r = 0.16$), Mn($r = -0.06$), Zn ($r = 0.03$), and Ni ($r = 0.09$). When S concentrations were above the 90th percentile, these correlations increased substantially: Fe ($r = 0.45$), Cu ($r = 0.35$), Mn ($r = 0.26$), Zn ($r = 0.42$), and Ni ($r = 0.41$). A similar pattern was observed for OP^{AA}, with stronger correlations between OP^{AA} and metals at higher S concentrations. For OP^{DTT}, correlations with metals did not change as dramatically across levels of S content, but OP^{DTT} was more strongly correlated with OP^{GSH} when S was higher ($r = 0.16$ vs. $r = 0.44$) (Figure S1). Figure 3 highlights how OP^{GSH} and OP^{AA} values varied across values of both metal (i.e., Fe, Cu, Zn) and S content in $PM_{2.5}$. These relationships were generally nonlinear with concave shapes for both OP^{GSH} and OP^{AA} except for the plot for OP^{AA}, Cu, and S, which was nearly linear with a steeper slope observed between OP^{AA} and Cu than between OP^{AA} and S.

Overall, daily mean $PM_{2.5}$ mass concentrations were weakly associated with acute cardiovascular events (OR = 1.015, 95% CI: 1.005, 1.025) with positive associations limited to men (OR = 1.025, 95% CI: 1.014, 1.036) and no association observed among women (OR = 0.999, 95% CI: 0.979, 1.019) (interaction *p*-value for lag-0 $PM_{2.5}$ and sex = 0.027) (Table S2). Among men, the magnitude of this risk was similar among younger (<70 y) (OR = 1.023, 95% CI: 1.004, 1.042) and older men

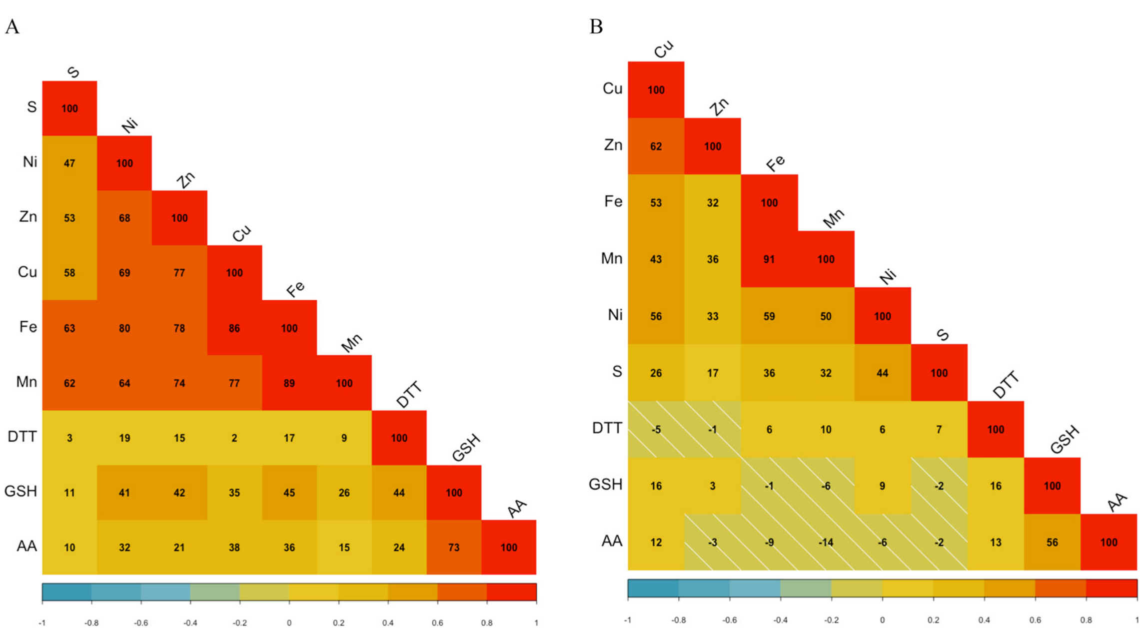

Figure 2. Spearman correlations between monthly mean oxidative potential [glutathione (OP^{GSH}), dithiothreitol (OP^{DTT}), and ascorbate (OP^{AA}) depletion (pmol/min/μg)] and transition metal concentrations (Canada, 2016–2017) [copper (Cu), iron (Fe), manganese (Mn), nickel (Ni), and zinc (Zn) in nanograms per cubic meter] at high (≥90th) (A) and low (<50th) (B) sulfur (S) concentrations.

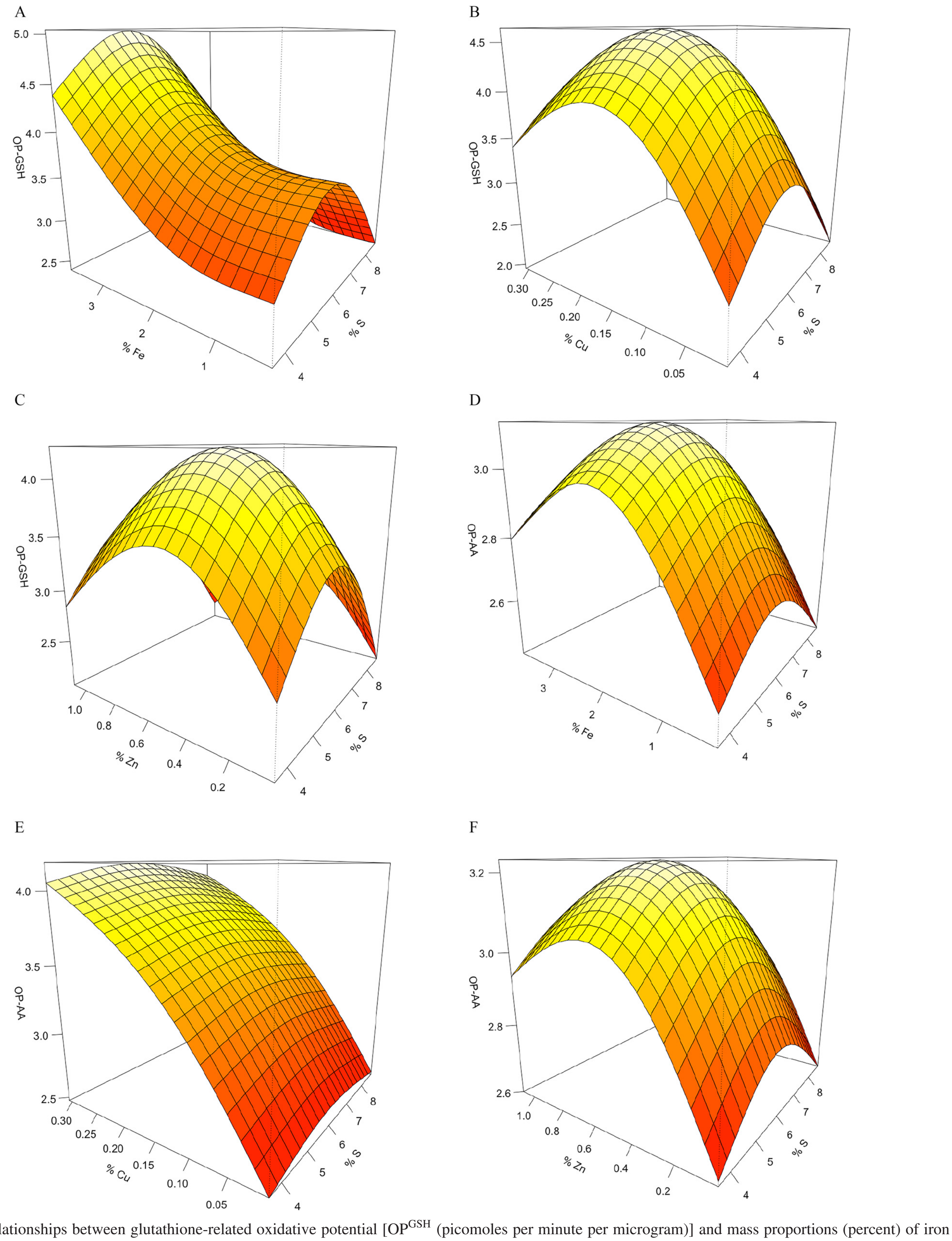

Figure 3. Relationships between glutathione-related oxidative potential [OP^{GSH} (picomoles per minute per microgram)] and mass proportions (percent) of iron (Fe) (A), copper (Cu) (B), zinc (Zn) (C), and sulfur (S) in $PM_{2.5}$ when the mass proportion of S is above the median (Canada, 2016–2017). Plots for ascorbate-related oxidative potential (OP^{AA}) are shown in panels (D), (E), and (F).

(OR = 1.028, 95% CI: 1.004, 1.052) (Table S2). When analyses were conducted across strata of transition metal and S content in $PM_{2.5}$, a consistent pattern of stronger associations was observed among men when *both* transition metal and S content were elevated. For example, an OR of 1.078 (95% CI: 1.049, 1.108) (per 10 $\mu g/m^3$) was observed for cardiovascular events in men when both Cu and S were above the median, whereas a weaker association was observed when both elements were below

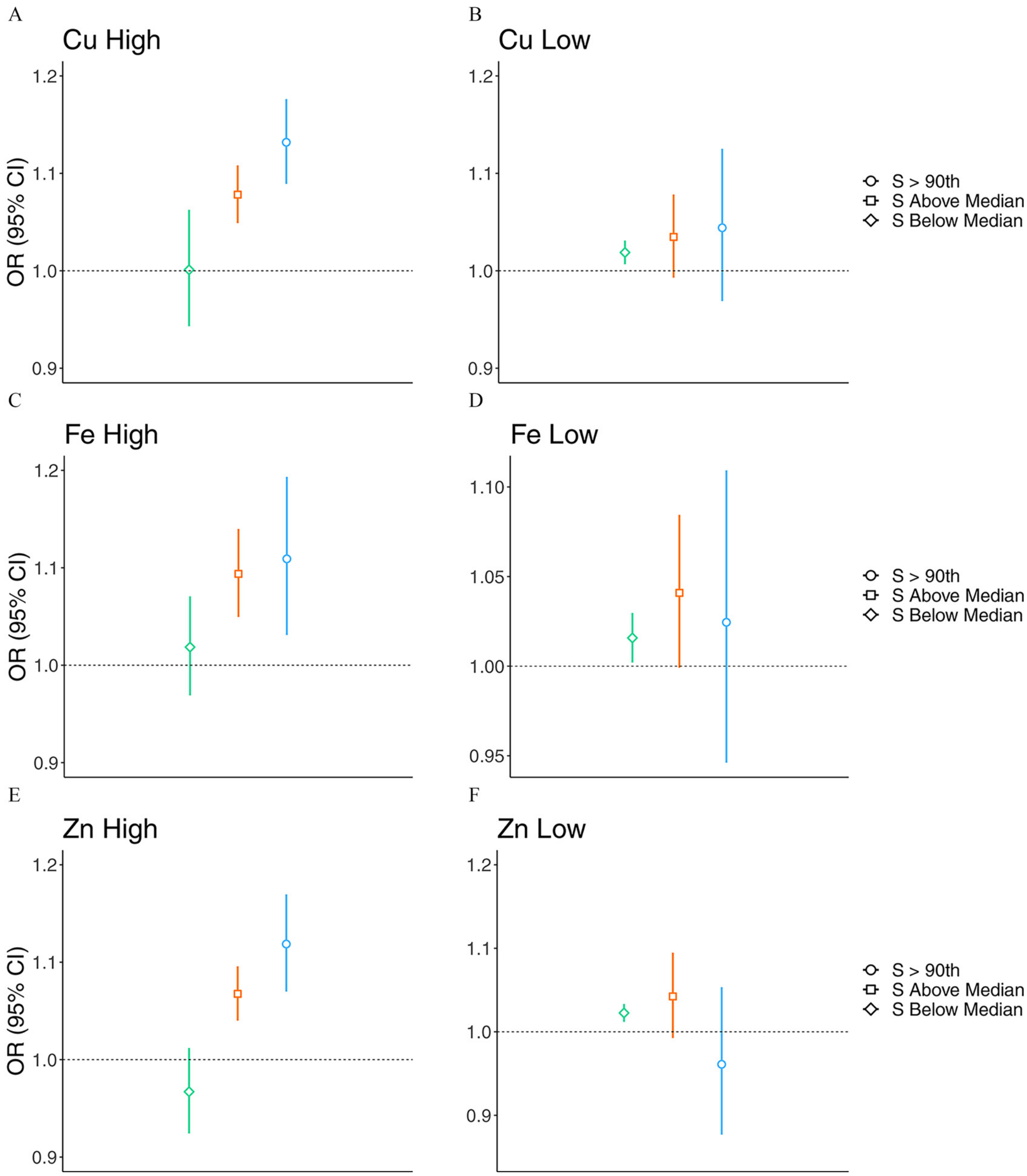

Figure 4. Variations in the strength of associations between lag-0 $PM_{2.5}$ (per 10 $\mu g/m^3$) and acute cardiovascular events among men across categories of mass proportions of sulfur (S) and copper (Cu) (A) and (B), iron (Fe) (C) and (D), and zinc (Zn) (E) and (F) in $PM_{2.5}$. All conditional logistic regression models are adjusted for lag-0 mean temperature and O_x. High and Low refer to mass proportions above (>50th) and below (≤50th) median values. See Table S4 for corresponding numeric data.

median values (OR = 1.019, 95% CI: 1.007, 1.031) (Table S4). This trend is shown in Figure 4 for Fe, Cu, and Zn, and complete results are shown in Table S4. When metal concentrations were above median values, *p*-values for interaction terms between lag-0 $PM_{2.5}$ and an indicator variable for S content (i.e., above/below median values) were 0.076 for Mn, 0.045 for Cu, and 0.00037 for Zn (Table S4). S content did not modify associations between $PM_{2.5}$ and acute cardiovascular events in men when metal concentrations were below median values (Table S4). A similar pattern was not observed in women, and in several cases $PM_{2.5}$ was inversely associated with hospital admissions for acute cardiovascular outcomes among women (Table S5). Within strata of S (i.e., above/below median values), interaction *p*-values between lag-0 $PM_{2.5}$ and metals among men were as follows: Cu (high S: 0.12; low S: 0.67); Fe (high S: 0.31; low S: 0.85); Mn (high S: 0.33; low S: 0.50); Ni (high S: 0.24; low S: 0.59); Zn (high S: 0.39; low S: 0.024). In models examining three-way interactions between lag-0 $PM_{2.5}$, metals (above/below median), and S (above/below median) in men, *p*-values for the three-way interaction terms were as follows: Cu (0.22), Fe (0.61), Ni (0.93), Mn (0.37), and Zn (0.054).

When analyses were conducted across strata of OP and S, a similar pattern was observed for all three assays, with the strongest associations among men occurring when both OP and S were elevated (there was no pattern among women) (Figure 5; Tables S4 and S5). When OP was above the median, S content modified associations between $PM_{2.5}$ and acute cardiovascular events among men for all three assays with interaction *p*-values of 0.010, 0.0052, and 0.0067 observed for OP^{GSH}, OP^{DTT}, and OP^{AA}, respectively. The strongest association was observed in the 90th percentile of S content when OP^{GSH} was high (OR = 1.164; 95% CI: 1.095, 1.237); $PM_{2.5}$ was weakly

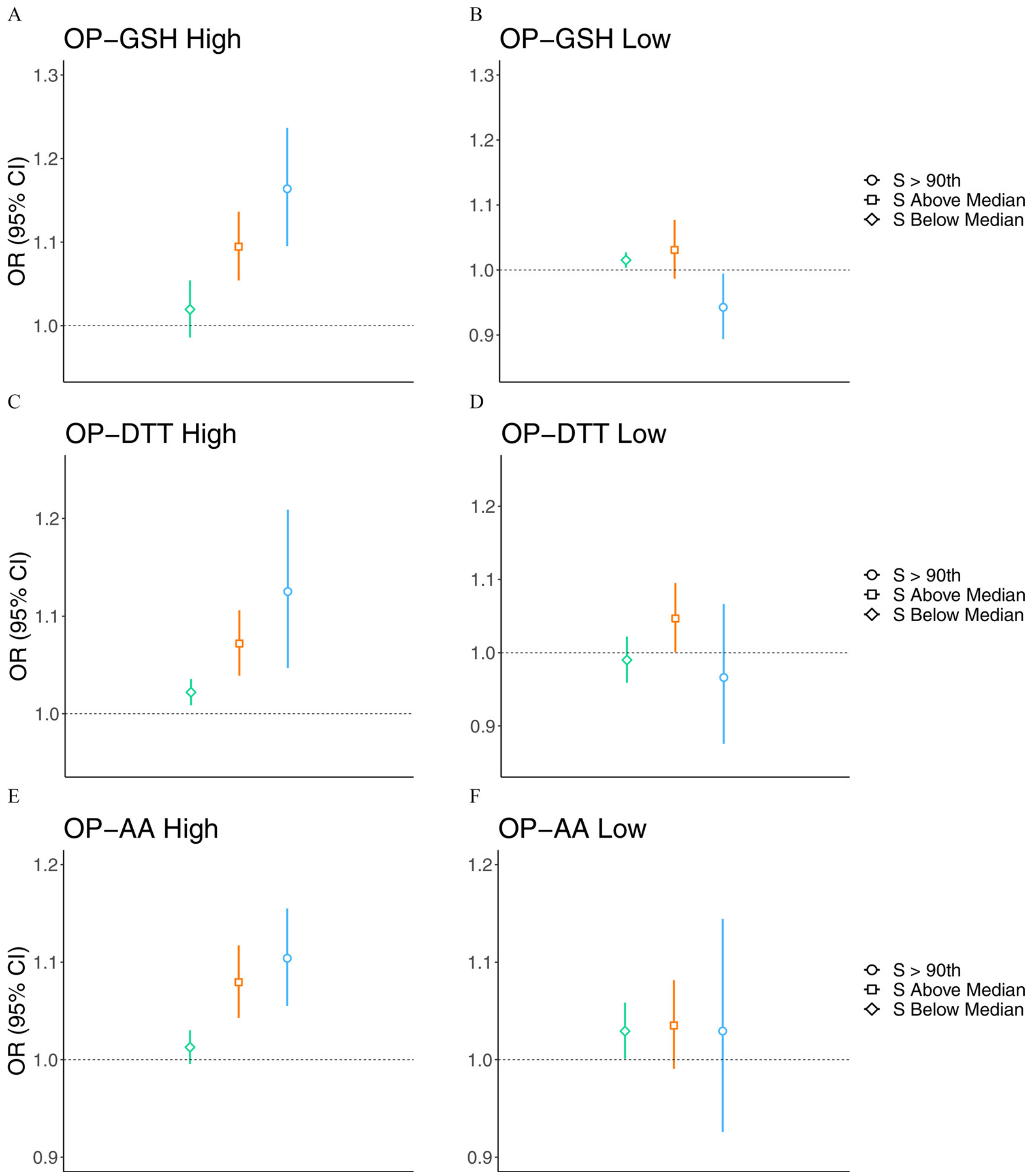

Figure 5. Variations in the strength of associations between lag-0 $PM_{2.5}$ (per $10\,\mu g/m^3$) and acute cardiovascular events among men across categories of mass proportions of sulfur (S) in $PM_{2.5}$ and glutathione (OP^{GSH}) (A) and (B), dithiothreitol (OP^{DTT}) (C) and (D), and ascorbate-related oxidative potential (OP^{AA}) (E) and (F) (Canada, 2016–2017). All conditional logistic regression models are adjusted for lag-0 mean temperature and O_x. High and Low refer to values above (>50th) and below (≤50th) median values. See Table S4 for corresponding numeric data.

associated with acute cardiovascular events when both S content and OP^{GSH} were below median values (OR = 1.015; 95% CI: 1.003, 1.027). Similar patterns were also observed for OP^{AA} and OP^{DTT} (Table S4). Interaction p-values for $PM_{2.5}$ and OP (above/below median) within strata of S mass proportions (above/below median) were as follows: OP^{GSH} (high S: 0.066; low S: 0.74); OP^{DTT} (high S: 0.59; low S: 0.12); OP^{AA} (high S: 0.18; low S: 0.32). Little evidence of effect modification by OP^{GSH}, OP^{DTT}, or OP^{AA} was observed among men in analyses not considering S content, although stronger associations were observed between $PM_{2.5}$ and acute cardiovascular events among men when OP^{GSH} (OP^{GSH} above median: OR = 1.039; 95% CI: 1.013, 1.065; OP^{GSH} below median: OR = 1.018; 95% CI: 1.006, 1.029) and OP^{DTT} (OP^{DTT} above median: OR = 1.028; 95% CI: 1.015, 1.042; OP^{DTT} below median: OR = 1.014; 95% CI: 0.984, 1.046) were elevated (Table S6). In models examining three-way interactions between lag-0 $PM_{2.5}$, OP (above/below median), and S (above/below median) in men, p-values for the three-way interaction terms were as follows: OP^{GSH} (0.16), OP^{DTT} (0.58), OP^{AA} (0.13).

Finally, given the observed pattern of stronger associations between outdoor $PM_{2.5}$ and acute cardiovascular events in men when both transition metal and S content were elevated, we also examined how the proportions of these components related to overall $PM_{2.5}$ mass concentrations. This question was of interest because if these proportions are not constant across $PM_{2.5}$ mass distributions, they could play a role determining the shape of concentration–response curves. These results are shown in Figure 6 and indicate that for a given mass proportion of metals in $PM_{2.5}$ (Fe and Cu in this example) the mass proportion of S increases as

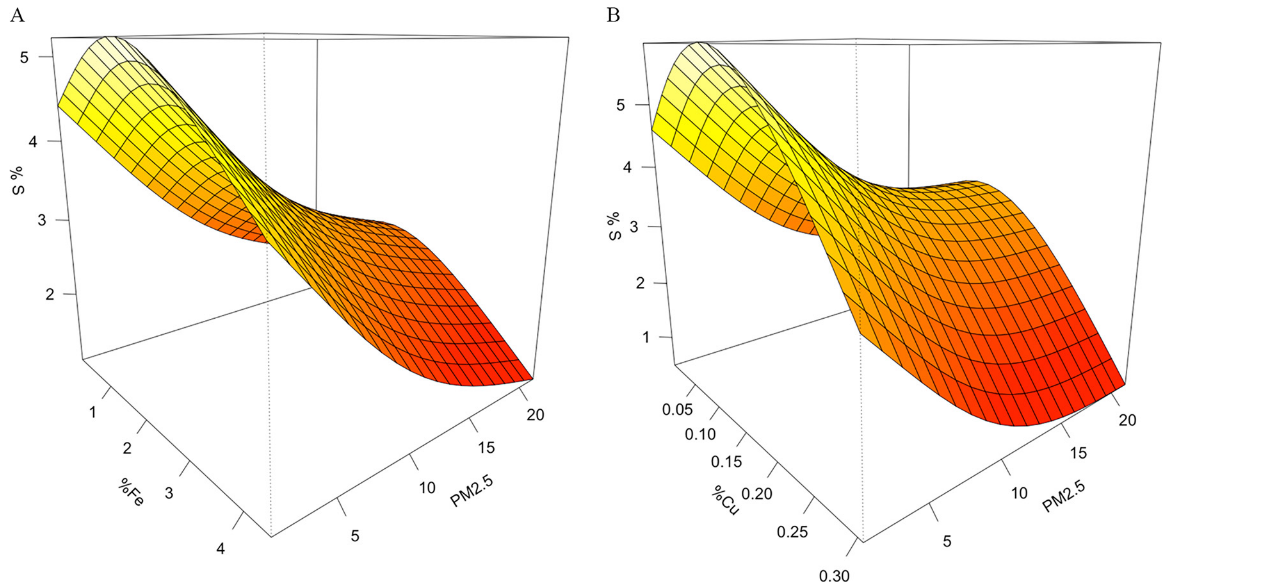

Figure 6. Generalized additive model plots for the mass proportion (percent) of sulfur (S), iron (Fe) (A), copper (Cu) (B), and $PM_{2.5}$ (Canada, 2016–2017). $PM_{2.5}$ mass concentrations (micrograms per cubic meter) are plotted up to the 99th percentile of monthly measurements.

$PM_{2.5}$ mass concentrations decrease. To verify that this pattern was not unique to Canada, we also downloaded data for $PM_{2.5}$ mass concentrations, Fe, Cu, and S for the year 2017 from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network in the United States (1,836 monthly averages values calculated using daily data) (IMPROVE 2021). As shown in Figure S2, for a given mass proportion of Cu/Fe, S mass proportions in $PM_{2.5}$ also increased as $PM_{2.5}$ mass concentrations decreased in the U.S. data.

Discussion

$PM_{2.5}$ is a complex mixture that varies in composition across both space and time. In this study, we examined the acute cardiovascular health impacts of $PM_{2.5}$ mass concentrations across strata of metals, OP, and S. Among men, outdoor $PM_{2.5}$ mass concentrations were most strongly associated with acute cardiovascular outcomes when mass proportions of both metals and S were elevated. A similar pattern was observed for OP and S. Moreover, OP appears to capture heterogeneity in $PM_{2.5}$ health effects among men because OP is more strongly associated with metals when the S content of $PM_{2.5}$ is higher. $PM_{2.5}$ was not associated with acute cardiovascular outcomes among women.

Recently, an increasing number of epidemiological studies have examined $PM_{2.5}$ OP as a complementary metric to traditional particle mass concentrations (Bates et al. 2019; Gao et al. 2020; Molina et al. 2020). To date, few studies have examined the role of oxidative potential in modifying the acute health impacts of $PM_{2.5}$. Specifically, we previously reported that OP^{GSH} modified associations between outdoor $PM_{2.5}$ mass concentrations and acute myocardial infarction (Weichenthal et al. 2016a), asthma (Weichenthal et al. 2016a), and airway inflammation in children with asthma (Maikawa et al. 2016). Similarly, two time-series studies noted stronger associations between OP^{DTT} and acute respiratory outcomes than for $PM_{2.5}$ (Bates et al. 2015; Abrams et al. 2017), but other studies have failed to replicate this finding (Atkinson et al. 2016). With respect to $PM_{2.5}$ composition, epidemiological evidence to date has been somewhat inconsistent (Schlesinger 2007; Lippmann 2014; Adams et al. 2015), and we have yet to conclusively identify specific components/sources of $PM_{2.5}$ that are most relevant to health. Nevertheless, a recent analysis of atmospheric particles suggests that combined transition metal and S content may influence the OP of $PM_{2.5}$ because sulfate increases particle acidity, which in turn increases metal dissolution and solubility, thus allowing metals to participate in redox reactions contributing to oxidative stress (Fang et al. 2017). Together, these mechanisms may help to explain spatiotemporal variations in the adverse health effects of $PM_{2.5}$, but epidemiological evidence in this area remains limited. In this study, we examined the combined impacts of transition metal, OP, and S content (as a marker for sulfate and indirectly metal solubility) on associations between outdoor $PM_{2.5}$ mass concentrations and the risk of acute cardiovascular events and noted several interesting findings.

First, the magnitudes of associations between daily mean outdoor $PM_{2.5}$ and acute cardiovascular outcomes in men were stronger when both transition metal *and* S content were elevated. In addition, evidence for effect modification was clearest across categories of S content when the transition metal content of $PM_{2.5}$ was elevated (particularly for Cu, Mn, and Zn). A similar pattern was apparent for OP, with stronger associations observed among men when both OP and S content were higher. Moreover, analysis of correlations between OP and transition metals at high and low S content suggested that OP and metals were more strongly correlated when S content was elevated. Therefore, our findings suggest that OP metrics may capture heterogeneity in the acute cardiovascular health impacts of $PM_{2.5}$ at least in part because they are more strongly associated with metals when S content is higher (i.e., when metal content appears to be most relevant to health). This finding was particularly true for OP^{GSH} and OP^{AA} and is consistent with previous evidence suggesting that these metrics are more strongly correlated with metals in $PM_{2.5}$ (e.g., Cu, Fe, Ni, Zn), whereas OP^{DTT} is more strongly related to organic components (e.g., organic carbon, water-soluble organic carbon) (Gao et al. 2020). In generalized additive model plots, nonlinear relationships were observed between transition metals, S, and OP, often with a convex shape (i.e., with OP peaking at certain mass proportions of metals and S). Although a detailed examination of particle chemistry was beyond the scope of this investigation, these plots suggest that component interactions influence overall $PM_{2.5}$ OP in a complex manner, and further investigation is needed to better understand these relationships because they may be useful in guiding future regulatory interventions.

Our analysis of transition metal and S content across the distribution of $PM_{2.5}$ mass concentrations indicates that for a given mass proportion of transition metals the mass proportion of S increases as $PM_{2.5}$ mass concentrations decrease. This finding could have important implications for future analyses of the shapes of concentration–response relationships for outdoor $PM_{2.5}$ mass concentrations. Specifically, if combined transition metal and S content are important determinants of $PM_{2.5}$-associated health impacts, one would expect to observe steeper increases in concentration–response curves at lower $PM_{2.5}$ concentrations. Indeed, patterns of steeper increases in concentrations–response curves at lower $PM_{2.5}$ concentrations have been reported around the world in time-series analyses of outdoor $PM_{2.5}$ and mortality (Liu et al. 2019) as well as in cohort studies of long-term exposures to outdoor $PM_{2.5}$ (Burnett et al. 2018; Christidis et al. 2019; Crouse et al. 2012, 2015; Pappin et al. 2019; Pinault et al. 2016, 2017), including pooled cohort study estimates used to estimate the global burden of disease attributable to outdoor air pollution (GBD 2019 Risk Factor Collaborators 2020). Although we could not specifically address this question in the current study, our findings combined with existing patterns of steeper concentration–response relationships at lower $PM_{2.5}$ mass concentrations in existing studies of outdoor $PM_{2.5}$ is intriguing. If confirmed, this hypothesis could shed new light on why we continue to see adverse health impacts of outdoor $PM_{2.5}$ at low mass concentrations and why these relationships tend to be stronger at the lower end of exposure distributions.

The combined importance of transition metals and sulfur in $PM_{2.5}$ is also interesting from the perspective of public health interventions. For example, it may be helpful to systematically identify regions (and time periods within regions) with elevated mass proportions of *both* components as a first step in prioritizing areas for future risk management activities. Moreover, it is possible that some threshold may exist for acute cardiovascular health impacts with respect to the relative proportions of S and transition metals in $PM_{2.5}$, but we did not have the power to examine this question in the present study. Sources of metals in $PM_{2.5}$ are diverse and include emissions from vehicles, industry, shipping, and brake wear (Bates et al. 2019; Birmili et al. 2006; Lough et al. 2005; Quiterio et al. 2004), whereas S (i.e., sulfate) primarily comes from point sources of fossil fuel combustion (e.g., coal-fired power plants for electricity generation) (Manoli et al. 2002; Moldanová et al. 2009; Oeder et al. 2015). The efficiency of targeting sources of metals or sulfate (or both) in a given region will depend on various logistical and economic considerations. However, in many cases the diverse nature of metal sources may make reductions in S concentrations more feasible. Importantly, if replicated in future analyses, our findings suggest that regulatory actions aimed at reducing sulfate may reduce the acute cardiovascular health impacts of $PM_{2.5}$ even if metal concentrations remain unchanged. Indeed, numerous previous regulations have targeted sources of S in $PM_{2.5}$, including limits on sulfur in gasoline (U.S. EPA 2021) and marine fuel oil (International Maritime Organization 2019), and our findings add strength to the justification for these regulatory actions from an environmental health perspective. More broadly, widespread integration of $PM_{2.5}$ composition/OP data into the risk assessment/risk management process will require new exposure models capable of estimating these parameters over broad spatiotemporal scales. Although models are currently available to predict large-scale variations in $PM_{2.5}$ components using remote sensing/chemical transport models (van Donkelaar et al. 2019; Xu et al. 2019), large-scale models for oxidative potential are only beginning to emerge (Daellenbach et al. 2020). Nevertheless, an increasing number of large-scale exposure models for OP are likely to be developed in the coming years as ground-level data support continues to increase over broad geographic areas.

Although this study had a number of important strengths, including prospective data collection for multiple OP metrics and $PM_{2.5}$ components across Canada, it is important to note several limitations. First, it was not possible to prospectively measure daily OP and $PM_{2.5}$ composition at multiple sites across Canada, and thus we relied on estimates of monthly mean composition and OP based on repeated 2-wk samples collected at each location. As a result, it is possible that a given month was misclassified with respect to composition and OP if the 2-wk measurement period was not representative of the true monthly average value. Moreover, this error could affect observed trends in risk estimates across strata of metals, S, and OP, making it more difficult to identify true patterns across strata (although findings were generally consistent across strata of all the components examined). Similarly, we could not identify which specific metals may be more or less harmful because all of the metals tended to be correlated and all demonstrated a similar pattern of increased risks at elevated metal and S content in $PM_{2.5}$. Likewise, we did not measure all possible time-varying factors potentially related to the outcome (i.e., stress), but it seems unlikely that these would be systematically related to daily $PM_{2.5}$ consistently within strata of metals/OP and S. In addition, the nature of our hypothesis required many models to be examined, and chance findings could have affected our results. However, given the consistency of the results among men, this seems like an unlikely explanation for the overall patterns observed.

A second limitation is related to our use of all cardiovascular outcomes as opposed to specific types of cardiovascular events (e.g., myocardial infarction). The use of all cardiovascular outcomes was necessary, given the relatively short time period under investigation, the fact that cases were limited to those living within 5 km of a $PM_{2.5}$ monitor (to reduce exposure misclassification, given high spatial variability for OP and metals) (Weichenthal et al. 2019), and the fact that monitoring was limited to many small to midsize cities that do not give rise to large numbers of cases. As a result, if $PM_{2.5}$ only contributes to an increased risk of specific types of acute cardiovascular events (e.g., Weichenthal et al. 2017), our analyses may underestimate the true magnitude of association between $PM_{2.5}$ and these specific outcomes. This aspect may be particularly relevant to our null findings among women because the use of all cardiovascular events may mask important associations with specific types of cardiovascular events among women. Indeed, although we observed clear and consistent patterns of associations between outdoor $PM_{2.5}$ and acute cardiovascular outcomes among men, $PM_{2.5}$ was not associated with acute cardiovascular events in women. We do not have an obvious explanation for this result, but it was consistent in all of the models we examined. Bell et al. (2015) also reported contrasting results between sexes (with a stronger association among women), but more generally our results highlight that sex-/gender-specific analyses should be more common in air pollution epidemiology because improved understanding of heterogeneity across sex/gender profiles may help to improve public health interventions and/or patient-level health information (Clougherty 2010).

Finally, our study was limited to the acute health impacts of $PM_{2.5}$, whereas long-term exposures are most important for overall burden of disease (GBD 2019 Risk Factor Collaborators 2020). However, our results highlight substantial spatiotemporal variations in outdoor $PM_{2.5}$ oxidative potential and composition across Canada, and future cohort studies could leverage this information to explore possible effect modification for outcomes, including cancer incidence and cause-specific/nonaccidental mortality. We previously addressed this question in a cohort study conducted in Ontario, Canada, and noted a stronger association between lung cancer mortality and $PM_{2.5}$ when OP^{GSH} was higher (Weichenthal et al. 2016c); however, future studies should aim to replicate these results on a larger scale.

In summary, our findings suggest that the mass proportions of transition metals and S play an important role in determining the strength of association between outdoor $PM_{2.5}$ and the risk of acute cardiovascular events in men. Moreover, our results indicate that OP metrics capture this trend in part because they are more strongly correlated with transition metals in $PM_{2.5}$ when S content is higher. These results provide new information on why we continue to see adverse health effects of $PM_{2.5}$ at low mass concentrations. Specifically, at a given mass proportion of metals, the mass proportion of S increased as $PM_{2.5}$ decreased; this finding may help to explain the repeated observation of steeper concentration–response relationships at the lower end of exposure distributions for $PM_{2.5}$. Identifying regions with elevated levels of both transition metal and S content in $PM_{2.5}$ may be an efficient means of prioritizing areas and sources for future regulatory interventions.

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References

Abrams JY, Weber RJ, Klein M, Sarnat SE, Chang HH, Strickland MJ, et al. 2017. Associations between ambient fine particulate oxidative potential and cardiorespiratory emergency department visits. Environ Health Perspect 125(10):107008, PMID: 29084634, https://doi.org/10.1289/EHP1545.

Achilleos S, Kioumourtzoglou MA, Wu CD, Schwartz JD, Koutrakis P, Papatheodorou SI. 2017. Acute effects of fine particulate matter constituents on mortality: a systematic review and meta-regression analysis. Environ Int 109:89–100, PMID: 28988023, https://doi.org/10.1016/j.envint.2017.09.010.

Adams K, Greenbaum DS, Shaikh R, van Erp AM, Russell AG. 2015. Particulate matter components, sources, and health: systematic approaches to testing effects. J Air Waste Manage Assoc 65(5):544–588, PMID: 25947313, https://doi.org/10.1080/10962247.2014.1001884.

Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. 2014. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax 69(7):660–665, PMID: 24706041, https://doi.org/10.1136/thoraxjnl-2013-204492.

Atkinson RW, Samoli E, Analitis A, Fuller GW, Green DC, Anderson HC, et al. 2016. Short-term associations between particle oxidative potential and daily mortality and hospital admissions in London. Int J Hyg Env Health 219(6):566–572, PMID: 27350257, https://doi.org/10.1016/j.ijheh.2016.06.004.

Baker MA, Cerniglia GJ, Zaman A. 1990. Microtiter plate assay for the measurement of glutathione and glutathione disulfide in large numbers of biological samples. Anal Biochem 190(2):360–365, PMID: 2291479, https://doi.org/10.1016/0003-2697(90)90208-Q.

Bates JT, Fang T, Verma V, Zeng L, Weber RJ, Tolbert PE, et al. 2019. Review of acellular assays of ambient particulate matter oxidative potential: methods and relationships with composition, sources, and health effects. Environ Sci Technol 53(8):4003–4019, PMID: 30830764, https://doi.org/10.1021/acs.est.8b03430.

Bates JT, Weber RJ, Abrams J, Verma V, Fang T, Klein M, et al. 2015. Reactive oxygen species generation linked to sources of atmospheric particulate matter and cardiorespiratory effects. Environ Sci Technol 49(22):13605–13612, PMID: 26457347, https://doi.org/10.1021/acs.est.5b02967.

Bell ML, Son JY, Peng RD, Wang Y, Dominici F. 2015. Ambient $PM_{2.5}$ and risk of hospital admissions. Do risks differ for men and women? Epidemiol 26(4):575–579, PMID: 25906368, https://doi.org/10.1097/EDE.0000000000000310.

Birmili W, Allen AG, Bary F, Harrison RM. 2006. Trace metal concentrations and water solubility in size-fractionated atmospheric particles and influence of road traffic. Environ Sci Technol 40(4):1144–1153, PMID: 16572768, https://doi.org/10.1021/es0486925.

Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope AC III, et al. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. PNAS 2018; 115:9592–9597, https://doi.org/10.1073/pnas.1803222115.

Charrier JG, Anastasio C. 2012. On dithiothreitol (DTT) as a measure of oxidative potential for ambient particles: evidence for the importance of soluble transition metals. Atmos Chem Phys 12(5):11317–11350, PMID: 23393494, https://doi.org/10.5194/acpd-12-11317-2012.

Cho AK, Sioutas C, Miguel AH, Kumagai Y, Schmitz DA, Singh M, et al. 2005. Redox activity of airborne particulate matter at different sites in the Los Angeles Basin. Environ Res 99(1):40–47, PMID: 16053926, https://doi.org/10.1016/j.envres.2005.01.003.

Christidis T, Erickson AC, Pappin AJ, Crouse DL, Pinault LL, Weichenthal SA, et al. 2019. Low concentrations of fine particle air pollution and mortality in the Canadian Community Health Survey cohort. Environ Health 18(1):84, PMID: 31601202, https://doi.org/10.1186/s12940-019-0518-y.

Clougherty JE. 2010. A growing role for gender analysis in air pollution epidemiology. Environ Health Perspect 118(2):167–176, PMID: 20123621, https://doi.org/10.1289/ehp.0900994.

Crouse DL, Peters PA, Hystad P, Brook JR, van Donkelaar A, Martin RV, et al. 2015. Ambient $PM_{2.5}$, O_3, and NO_2 exposures and associations with mortality over 16 years of follow-up in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Health Perspect 123(11):1180–1186, PMID: 26528712, https://doi.org/10.1289/ehp.1409276.

Crouse DL, Peters PA, van Donkelaar A, Goldberg MS, Villeneuve PJ, Brion O, et al. 2012. Risk of nonaccidental and cardiovascular mortality in relation to long-term exposure to low concentrations of fine particulate matter: a Canadian national-level cohort study. Environ Health Perspect 120(5):708–714, PMID: 22313724, https://doi.org/10.1289/ehp.1104049.

Daellenbach K, Uzu G, Jiang J, Cassagnes LE, Leni Z, Vlachou A, et al. 2020. Sources of particulate-matter air pollution and its oxidative potential in Europe. Nature 587(7834):414–419, PMID: 33208962, https://doi.org/10.1038/s41586-020-2902-8.

Fang T, Guo H, Zeng L, Verma V, Nenes A, Weber RJ. 2017. Highly acidic ambient particles, soluble metals, and oxidative potential: a link between sulfate and aerosol toxicity. Environ Sci Technol 51(5):2611–2620, PMID: 28141928, https://doi.org/10.1021/acs.est.6b06151.

Gao D, Ripley S, Weichenthal S, Godri Pollitt K. 2020. Ambient particulate matter oxidative potential: chemical determinants, associated health effects, and strategies for risk management. Free Radic Biol Med 151:7–25, PMID: 32430137, https://doi.org/10.1016/j.freeradbiomed.2020.04.028.

GBD 2019 Risk Factor Collaborators. 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396:1223–1249, PMID: 33069327, https://doi.org/10.1016/S0140-6736(20)30752-2.

Gibson D, Richards H, Chapman A. 2008. The national ambulatory care reporting system: factors that affect the quality of its emergency data. Int J Information Quality 2(2):97–114, https://doi.org/10.1504/IJIQ.2008.022958.

Godri KJ, Green DC, Fuller GW, Dall'Osto M, Beddows DC, Kelly FJ, et al. 2010. Particulate oxidative burden associated with firework activity. Environ Sci Technol 44(21):8295–8301, PMID: 20886897, https://doi.org/10.1021/es1016284.

Griffith OW. 1980. Determination of glutathione and glutathione disulfide using glutathione reductase and 2-Vinylpyridine. Anal Biochem 106(1):207–212, PMID: 7416462, https://doi.org/10.1016/0003-2697(80)90139-6.

IMPROVE (Interagency Monitoring of Protected Visual Environments). 2021. Data. http://vista.cira.colostate.edu/Improve/data-page/ [accessed 15 March 2021].

International Maritime Organization. 2019. IMO 2020–Cutting Sulfur Oxide Emissions. https://www.imo.org/en/MediaCentre/HotTopics/Pages/Sulfur-2020.aspx#:∼:text=Known%20as%20%E2%80%9CIMO%202020%E2%80%9D%2C,the%20previous%20limit%20of%203.5%25.&text=Before%20the%20entry%20into%20force,were%20using%20heavy%20fuel%20oil [accessed 15 March 2021].

Janes H, Sheppard L, Lumley T. 2005. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. Epidemiology 16(6):717–726, PMID: 16222160, https://doi.org/10.1097/01.ede.0000181315.18836.9d.

Künzli N, Schindler C. 2005. A call for reporting the relevant exposure term in air pollution case-crossover studies. J Epidemiol Community Health 59(6):527–530, PMID: 15911651, https://doi.org/10.1136/jech.2004.027391.

Lavigne É, Burnett RT, Stieb DM, Evans GJ, Godri Pollitt KJ, Chen H, et al. 2018. Fine particulate air pollution and adverse birth outcomes: effect modification by

regional nonvolatile oxidative potential. Environ Health Perspect 126(7):077012, PMID: 30073952, https://doi.org/10.1289/EHP2535.
Lippmann M. 2014. Toxicological and epidemiological studies of cardiovascular effects of ambient fine particulate matter ($PM_{2.5}$) and its chemical components: coherence and public health implications. Crit Rev Toxicol 44(4):299–347, PMID: 24494826, https://doi.org/10.3109/10408444.2013.861796.
Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, et al. 2019. Ambient particulate air pollution and daily mortality in 652 cities. N Engl J Med 381(8):705–715, PMID: 31433918, https://doi.org/10.1056/NEJMoa1817364.
Lough GC, Schauer JJ, Park JS, Shafer MM, DeMinter JT, Weinstein JP. 2005. Emissions of metals associated with motor vehicle roadways. Environ Sci Technol 39(3):826–836, PMID: 15757346, https://doi.org/10.1021/es048715f.
Maikawa CL, Weichenthal S, Wheeler AJ, Dobbin NA, Smargiassi A, Evans G, et al. 2016. Particulate oxidative burden as a predictor of exhaled nitric oxide in children with asthma. Environ Health Perspect 124(10):1616–1622, PMID: 27152705, https://doi.org/10.1289/EHP175.
Manoli E, Voutsa D, Samara C. 2002. Chemical characterization and source identification/apportionment of fine and coarse air particles in Thessaloniki, Greece. Atmos. Environ 36(6):949–961, https://doi.org/10.1016/S1352-2310(01)00486-1.
Ministère de la Santé et des Services Sociaux. 2021. MED-ÉCHO–Hospitalisations et chirurgies d'un jour dans les centres hospitaliers du Québec. Ministère de la Santé et des Services sociaux. https://www.msss.gouv.qc.ca/professionnels/statistiques-donnees-services-sante-services-sociaux/med-echo-hospitalisations-et-chirurgies-d-un-jour-dans-les-centres-hospitaliers-du-quebec/ [accessed 28 March 2021].
Moldanová J, Fridell E, Popovicheva O, Demirdjian B, Tishkova V, Faccinetto A, et al. 2009. Characterisation of particulate matter and gaseous emissions from a large ship diesel engine. Atmos Environ 43(16):2632–2641, https://doi.org/10.1016/j.atmosenv.2009.02.008.
Molina C, Toro A R, Manzano C, Canepari S, Massimi L, Leiva-Guzmán M. 2020. Airborne aerosols and human health: leapfrogging from mass concentration to oxidative potential. Atmosphere 11(9):917, https://doi.org/10.3390/atmos11090917.
Mudway IS, Stenfors N, Duggan ST, Roxborough H, Zielinski H, Marklund SL, et al. 2004. An in vitro and in vivo investigation of the effects of diesel exhaust on human airway lining fluid antioxidants. Arch Biochem Biophys 423(1):200–212, PMID: 14871482, https://doi.org/10.1016/j.abb.2003.12.018.
Oeder S, Kanashova T, Sippula O, Sapcariu SC, Streibel T, Arteaga-Salas JM, et al. 2015. Particulate matter from both heavy fuel oil and diesel fuel shipping emissions show strong biological effects on human lung cells at realistic and comparable in vitro exposure conditions. PLoS One 10(6):e0126536, PMID: 26039251, https://doi.org/10.1371/journal.pone.0126536.
Pappin AJ, Christidis T, Pinault LL, Crouse DL, Brook JR, Erickson AC, et al. 2019. Examining the shape of the association between low levels of fine particulate matter and mortality across three cycles of the Canadian Census Health and Environment Cohort. Environ Health Perspect 127(10):107008, PMID: 31638837, https://doi.org/10.1289/EHP5204.
Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, et al. 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian Community Health Survey cohort. Environ Health 15:18, PMID: 26864652, https://doi.org/10.1186/s12940-016-0111-6.
Pinault L, Weichenthal S, Crouse DL, Brauer M, Erickson A, van Donkelaar A, et al. 2017. Associations between fine particulate matter and mortality in the 2001 Canadian Census Health and Environment Cohort. Environ Res 159:406–415, PMID: 28850858, https://doi.org/10.1016/j.envres.2017.08.037.
Quiterio SL, Sousa da Silva CR, Arbilla G, Escaleira V. 2004. Metals in airborne particulate matter in the industrial district of Santa Cruz, Rio De Janeiro, in an annual period. Atmos. Environ 38(2):321–331, https://doi.org/10.1016/j.atmosenv.2003.09.017.
Rao X, Zhong J, Brook RD, Rajagopalan S. 2018. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. Antioxid Redox Signal 28(9):797–818, PMID: 29084451, https://doi.org/10.1089/ars.2017.7394.
Schlesinger RB. 2007. The health impact of common inorganic components of fine particulate ($PM_{2.5}$) in ambient air: a critical review. Inhal Toxicol 19(10):811–832, PMID: 17687714, https://doi.org/10.1080/08958370701402382.
U.S. EPA (U.S. Environmental Protection Agency). 2021. Gasoline Standards: Gasoline Sulfur. https://www.epa.gov/gasoline-standards/gasoline-sulfur#:~:text=Sulfur%20is%20a%20natural%20component,controls%20and%20reduces%20air%20pollution [accessed 15 March 2021].
van Donkelaar A, Martin RV, Li C, Burnett RT. 2019. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. Environ Sci Technol 53(5):2595–2611, PMID: 30698001, https://doi.org/10.1021/acs.est.8b06392.
Verma V, Fang T, Guo H, King L, Bates JT, Peltier RE, et al. 2014. Reactive oxygen species associated with water-soluble $PM_{2.5}$ in the southeastern United States: spatiotemporal trends and source apportionment. Atmos Chem Phys 14(23):12915–12930, https://doi.org/10.5194/acp-14-12915-2014.
Weichenthal S, Crouse DL, Pinault L, Godri-Pollitt K, Lavigne E, Evans E, et al. 2016c. Oxidative burden of fine particulate air pollution and risk of cause-specific mortality in the Canadian Census Health and Environment Cohort (CanCHEC). Environ Res 146:92–99, PMID: 26745732, https://doi.org/10.1016/j.envres.2015.12.013.
Weichenthal S, Kulka R, Lavigne E, van Rijswijk D, Brauer M, Villeneuve PJ, et al. 2017. Biomass burning as a source of ambient fine particulate air pollution and acute myocardial infarction. Epidemiol 28:329–337, PMID: 28177951, https://doi.org/10.1097/EDE.0000000000000636.
Weichenthal S, Lavigne E, Evans GJ, Godri Pollitt KJ, Burnett R. 2016b. Fine particulate matter and emergency room visits for respiratory illness: effect modification by oxidative potential. Am J Respir Crit Care Med 194(5):577–586, PMID: 26963193, https://doi.org/10.1164/rccm.201512-2434OC.
Weichenthal S, Lavigne E, Evans G, Pollitt K, Burnett RT. 2016a. Ambient PM2.5 and risk of emergency room visits for myocardial infarction: impact of regional $PM_{2.5}$ oxidative potential: a case-crossover study. Environ Health 15:46, PMID: 27012244, https://doi.org/10.1186/s12940-016-0129-9.
Weichenthal S, Shekarrizfard M, Traub A, Kulka R, Al-Rijleh K, Anowar S, et al. 2019. Within-city spatial variations in multiple measures of $PM_{2.5}$ oxidative potential in Toronto, Canada. Environ Sci Technol 53(5):2799–2810, PMID: 30735615, https://doi.org/10.1021/acs.est.8b05543.
Wood S. 2021. Mixed GAM Computation Vehicle with Automatic Smoothness Estimation. https://cran.r-project.org/web/packages/mgcv/mgcv.pdf [accessed 14 March 2021].
Xu JW, Martin RV, Henderson BH, Meng J, Oztaner B, Hand JL, et al. 2019. Simulation of airborne trace metals in fine particulate matter over North America. Atmos Environ 214:116883, PMID: 32665763, https://doi.org/10.1016/j.atmosenv.2019.116883.
Yang Y, Ruan Z, Wang X, Yang Y, Mason TG, Lin H, et al. 2019. Short-term and long-term exposures to fine particulate matter constituents and health: a systematic review and meta-analysis. Environ Pollut 247:874–882, PMID: 30731313, https://doi.org/10.1016/j.envpol.2018.12.060.