

## ORIGINAL ARTICLE

# Within-City Variation in Reactive Oxygen Species from Fine Particle Air Pollution and COVID-19

David M. Stieb<sup>1,2</sup>, Greg J. Evans<sup>3</sup>, Teresa M. To<sup>4,5</sup>, Pascale S. J. Lakey<sup>6</sup>, Manabu Shiraiwa<sup>6</sup>, Marianne Hatzopoulou<sup>7</sup>, Laura Minet<sup>7</sup>, Jeffrey R. Brook<sup>3,4</sup>, Richard T. Burnett<sup>2</sup>, and Scott A. Weichenthal<sup>8,9</sup>

<sup>1</sup>Environmental Health Science and Research Bureau and <sup>9</sup>Water and Air Quality Bureau, Health Canada, Ottawa, Ontario, Canada; <sup>2</sup>School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada; <sup>3</sup>Department of Chemical Engineering, <sup>4</sup>Dalla Lana School of Public Health, and <sup>7</sup>Department of Civil and Mineral Engineering, University of Toronto, Toronto, Ontario, Canada; <sup>5</sup>Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada; <sup>6</sup>Department of Chemistry, University of California Irvine, Irvine, California; and <sup>8</sup>Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

## Abstract

**Rationale:** Evidence linking outdoor air pollution with coronavirus disease (COVID-19) incidence and mortality is largely based on ecological comparisons *between* regions that may differ in factors such as access to testing and control measures that may not be independent of air pollution concentrations. Moreover, studies have yet to focus on key mechanisms of air pollution toxicity such as oxidative stress.

**Objectives:** To conduct a *within-city* analysis of spatial variations in COVID-19 incidence and the estimated generation of reactive oxygen species (ROS) in lung lining fluid attributable to fine particulate matter (particulate matter with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$  [ $\text{PM}_{2.5}$ ]).

**Methods:** Sporadic and outbreak-related COVID-19 case counts, testing data, population data, and sociodemographic data for 140 neighborhoods were obtained from the City of Toronto. ROS estimates were based on a mathematical model of ROS generation

in lung lining fluid in response to iron and copper in  $\text{PM}_{2.5}$ . Spatial variations in long-term average ROS were predicted using a land-use regression model derived from measurements of iron and copper in  $\text{PM}_{2.5}$ . Data were analyzed using negative binomial regression models adjusting for covariates identified using a directed acyclic graph and accounting for spatial autocorrelation.

**Measurements and Main Results:** A significant positive association was observed between neighborhood-level ROS and COVID-19 incidence (incidence rate ratio = 1.07; 95% confidence interval, 1.01–1.15 per interquartile range ROS). Effect modification by neighborhood-level measures of racialized group membership and socioeconomic status was also identified.

**Conclusions:** Examination of neighborhood characteristics associated with COVID-19 incidence can identify inequalities and generate hypotheses for future studies.

**Keywords:** air pollution; COVID-19; oxidative stress

Evidence from multiple lines of research, including toxicology, human clinical studies, and epidemiology, suggests that outdoor air pollution exposure increases the risk of

respiratory infection (1). Both short-term and long-term exposures are associated with morbidity and mortality from respiratory infections (2–6), and there is evidence that air

pollution exposure adversely affects respiratory and systemic immune defenses (3, 7), including increased epithelial expression of receptors for respiratory viruses (8). Oxidative

(Received in original form November 11, 2020; accepted in final form April 2, 2021)

©This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (<https://creativecommons.org/licenses/by-nc-nd/4.0/>). For commercial usage and reprints, please contact Diane Gern ([dgern@thoracic.org](mailto:dgern@thoracic.org)).

M.S. is supported by funding from the Health Effects Institute (4964-RFA17-3/18-6).

Author Contributions: Conception and design: D.M.S., G.J.E., T.M.T., P.S.J.L., M.S., M.H., L.M., J.R.B., R.T.B., and S.A.W. Data acquisition: D.M.S., P.S.J.L., M.S., M.H., L.M., and S.A.W. Analysis and interpretation: D.M.S., G.J.E., T.M.T., M.H., L.M., R.T.B., and S.A.W. Drafting the manuscript for important intellectual content: D.M.S., G.J.E., P.S.J.L., M.S., J.R.B., and S.A.W. All authors approved the manuscript.

Correspondence and requests for reprints should be addressed to David M. Stieb, M.D., M.Sc., 420-757 West Hastings Street, Vancouver, BC, V6C 1A1 Canada. E-mail: [dave.stieb@canada.ca](mailto:dave.stieb@canada.ca).

This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of content online at [www.atsjournals.org](http://www.atsjournals.org).

Am J Respir Crit Care Med Vol 204, Iss 2, pp 168–177, Jul 15, 2021

Copyright © 2021 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.202011-4142OC on April 2, 2021

Internet address: [www.atsjournals.org](http://www.atsjournals.org)

## At a Glance Commentary

### Scientific Knowledge on the

**Subject:** It is well established that air pollution is associated with morbidity and mortality from respiratory infections, and adversely affects respiratory and systemic immune defenses. Oxidative stress appears to be a key pathophysiological mechanism. Although the body of evidence linking air pollution exposure and coronavirus disease (COVID-19) incidence and mortality is growing rapidly, several methodological shortcomings of existing studies have been identified. In particular, many studies have relied on ecological comparisons *between* regions that may differ in factors such as access to testing and control measures that may not be independent of air pollution concentrations. Studies have yet to focus on key mechanisms of air pollution toxicity, such as oxidative stress.

### What This Study Adds to the Field:

This study contributes to public health evidence on COVID-19 by conducting a *within-city* analysis in order to identify neighborhood characteristics associated with COVID-19 incidence and potential inequalities in the effects of air pollution. By employing a novel exposure metric reflecting reactive oxygen species generation in human lung epithelial lining fluid attributable to transition metals in fine particle air pollution, the study highlights a key mechanistic pathway. Additional research employing individual-level data is needed to elaborate causal pathways.

stress has been identified as a key pathophysiological mechanism linking air pollution exposure and adverse health effects (9) and, more specifically, viral respiratory infection (10). However, few epidemiological studies have employed exposure metrics specifically reflecting this mechanism (9).

Evidence related to air pollution and novel coronaviruses is limited. Evidence from

the severe acute respiratory syndrome coronavirus 1 outbreak suggests that exposure to air pollution increased transmission (11) and worsened prognosis (12, 13). Emerging evidence suggests that novel coronavirus disease (COVID-19) incidence and mortality may be increased in relation to both acute (14, 15) and chronic air pollution exposure (16–22). Disproportionate impacts of COVID-19 on racialized groups have been identified (23–26), and it has been hypothesized that greater exposure to air pollution could partially mediate these disproportionate impacts (25, 27).

Although the body of evidence is growing rapidly, several methodological shortcomings of existing studies have been identified, including reliance on ecological comparisons *between* regions that may differ in important ways (e.g., access to testing and implementation of control measures) that may not be independent of outdoor air pollution concentrations; application of inappropriate statistical models for count data; and failure to account for spatial clustering or examine effect modification (28). To address these shortcomings, we conducted a *within-city* analysis of associations between air pollution exposure and COVID-19 incidence among 140 neighborhoods in Toronto, Canada. We employed a novel indicator of reactive oxygen species (ROS) generation in human lung epithelial lining fluid (ELF) attributable to transition metals in fine particulate matter (particulate matter with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$  [ $\text{PM}_{2.5}$ ]) (29, 30) as the primary exposure variable, to address the lack of evidence pertaining to exposure metrics specifically reflecting oxidative stress. Other exposures considered were  $\text{PM}_{2.5}$  mass, nitrogen dioxide ( $\text{NO}_2$ ), and greenness. In contrast to earlier studies, in the present analysis, we differentiate between sporadic and outbreak-related cases, apply a statistical model (negative binomial) appropriate for count data, account for spatial clustering, examine effect modification by neighborhood characteristics, and incorporate neighborhood-level testing as a covariate. Our within-city analysis is also not confounded by between-city variability in the nature and timing of public health measures.

## Methods

### Neighborhood-Level COVID-19 Data

COVID-19 case counts through October 12, 2020, were obtained from the City of Toronto

(31). Outbreak-related cases refer to those occurring in healthcare institutions, including both acute care and long-term care facilities, and other communal settings such as homeless shelters, whereas all other cases are considered sporadic (31). We also obtained data on days elapsed since the first case, days since peak daily incidence of cases, case outcomes, and weekly rates of COVID-19 testing (the latter is from August 30, 2020, onward only) (31).

### ROS Exposure Data

Concentrations of ROS generated in human lung ELF were estimated using a kinetic model of mass transport and chemical reactions of iron and copper in  $\text{PM}_{2.5}$  with antioxidants and surfactants in ELF (29, 30). Spatial variations in annual mean ROS were based on a land-use regression model derived from 2-week average concentrations of iron and copper in  $\text{PM}_{2.5}$  at 81 unique sites in Toronto in the summer of 2016 and the winter of 2017 (29). Further details on ROS and other exposures are described in Text E1 in the online supplement. Exposure data were mapped to census dissemination area ( $n = 3,691$ ) and population weighted to the neighborhood level in R (32) using GISTools (33), *rgdal* (34), and *raster* (35) packages.

### Sociodemographic Data

Neighborhood-level population counts and sociodemographic data from the 2016 census for factors potentially affecting COVID-19 incidence (23, 26, 31, 36) were obtained from the City of Toronto (37). These variables included measures of age distribution (percentage of population 65 years of age or older and 85 years of age or older), socioeconomic status (SES) (percentage unemployed, with less than high school education, or with income less than the low-income cutoff or low-income measure), racialized group membership (percentage Black, South Asian, visible minority, or non-English or French speakers), and potential risk factors for COVID-19 transmission (percentage of users of public transit for commuting, percentage living in unsuitable [crowded] housing, and percentage in a health occupation or health and social service industry).

### Statistical Analysis

Negative binomial regression was used to model the relationship between air pollution concentrations and COVID-19 cases by neighborhood, with the logarithm of

**Table 1.** Characteristics of COVID-19 Cases

	Sporadic		Outbreak Related	
	n	Percentage	n	Percentage
Cases	16,415	100.0	6,646	100.0
Cases missing neighborhood	481	2.9	273	4.1
Cases with neighborhood*	15,934	97.1	6,373	95.9
Fatal	256	1.6	1,032	16.2
Hospitalized	1,293	8.1	826	13.0
Admitted to intensive care	359	2.3	79	1.2
Intubated	243	1.5	47	0.7
Sex, F	7,704	48.6	3,973	63.9
Sex, M	8,149	51.4	2,240	36.0
Sex missing	73	0.4	158	2.4
Age <50 yr	10,829	68.0	1,955	30.7
Age ≥50 yr	5,084	32.0	4,414	69.3
Age ≥60 yr	2,626	16.5	3,632	57.0

Definition of abbreviation: COVID-19 = coronavirus disease.

\*Used as denominator for calculation of percentages in subsequent rows.

neighborhood population as an offset. Model covariates were selected using the directed acyclic graph (DAG) (38) shown in Figure E1 in the online supplement. Specifically, all models were adjusted for neighborhood-level measures of racialized group membership, SES, risk factors for COVID-19 transmission, and community

transmission (number of days since peak daily case count and since first case). The presence of residual spatial autocorrelation was examined by mapping model residuals and computing Moran's I (39). If significant spatial autocorrelation was detected, spatial regression was conducted, adding the average of nearest neighbor incidence as a

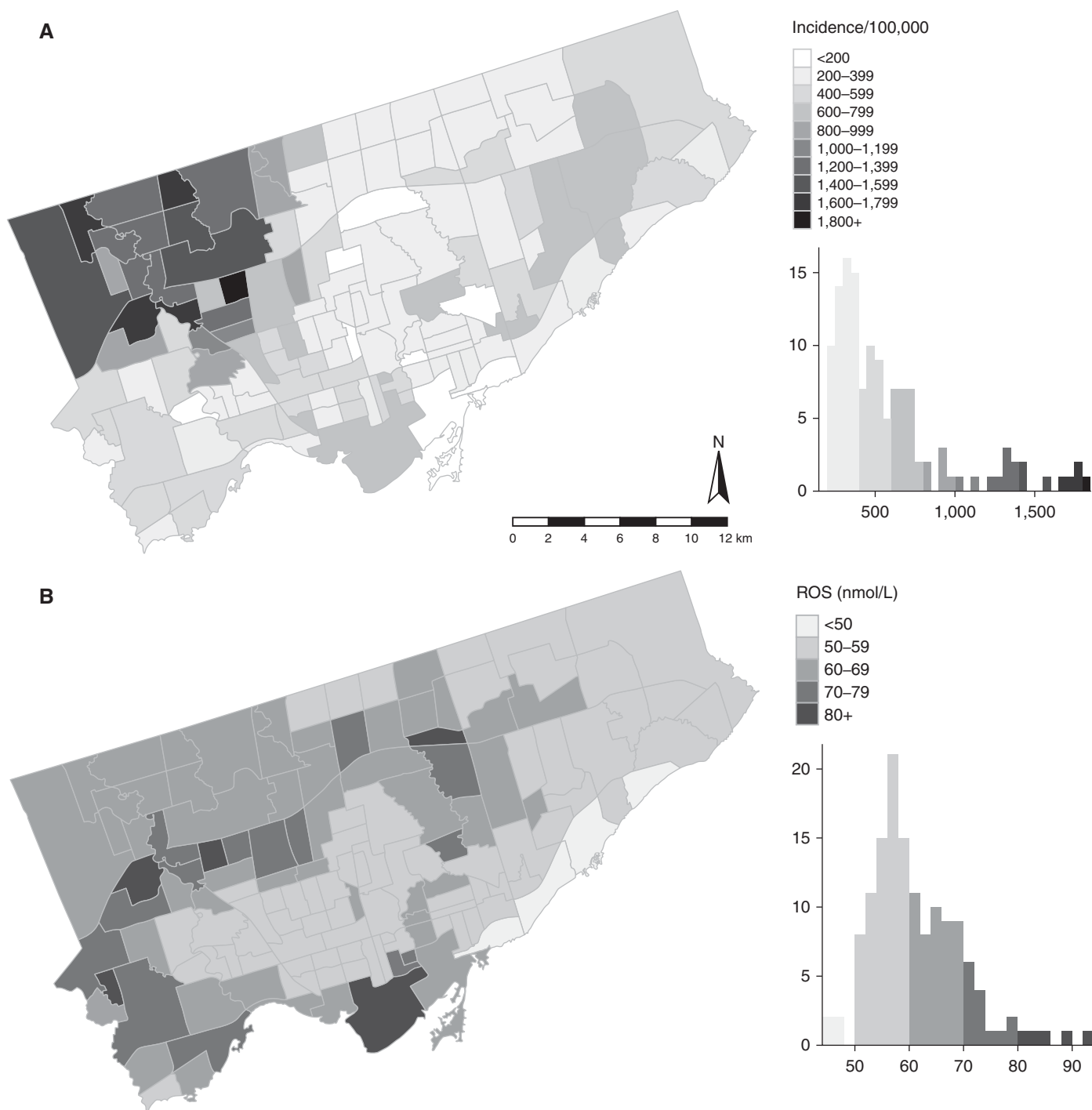
covariate (40). Analysis was conducted in R (32) using the lme4 (41), MASS (42), mgcv (43), and spatialreg (40) packages.

Additional methodological details are provided in Text E1 in the online supplement. Research ethics board approval was not required, as all data are publicly available.

**Table 2.** Distribution of Cases, Environmental Exposures, and Sociodemographic Characteristics among Toronto Neighborhoods

Characteristic	Minimum	Percentile			Maximum
		25th	50th	75th	
Sporadic cases to October 12	13	45.5	78.0	138.0	585.0
Days since peak incidence	1	5	12	32	210
Days since first case	186	202	209	214	263
Tests/1,000 population (August 30 to October 10)	40.7	69.2	84.2	107.1	142.8
2016 population	6,577	12,020	16,750	23,855	65,913
Population density per km <sup>2</sup>	1,040	3,595	5,072	7,621	44,321
Land area, km <sup>2</sup>	0.0	2.0	3.0	5.0	37.0
PM <sub>2.5</sub> , µg/m <sup>3</sup>	6.5	7.0	7.3	7.4	7.8
NO <sub>2</sub> , ppb	8.8	14.0	15.0	16.0	20.9
ROS, nmol/L	44.7	55.9	59.4	66.3	93.5
NDVI >0	0.3	0.5	0.6	0.6	0.7
Age ≥65 yr, %	4.8	13.4	15.4	18.2	28.0
Age ≥85 yr, %	0.3	1.6	2.2	3.1	8.7
Black, %	0.9	3.5	5.7	11.4	35.4
South Asian, %	1.3	3.7	6.2	14.1	47.2
People of color, %	12.0	27.7	42.9	67.0	96.6
Non-English or French speakers, %	0.2	2.2	3.6	5.9	26.9
Below low-income cutoff, %	4.1	12.8	16.3	20.2	36.4
Below low-income measure, %	4.5	14.1	18.6	24.0	45.5
Less than high school education, %	2.9	10.7	16.4	21.3	39.1
Commute by public transit, %	18.0	31.6	37.6	43.0	63.7
Crowded housing, %	1.5	6.9	10.9	15.9	42.2
Unemployed, %	4.5	6.9	8.2	9.6	14.6
Not moved in the last 5 yr, %	26.3	57.2	62.9	67.6	77.9
Health occupation, %	2.6	4.7	5.4	6.2	12.0
Health and social assistance industry, %	6.6	8.5	9.5	10.7	16.2

Definition of abbreviations: NDVI = normalized difference vegetation index (greenness); NO<sub>2</sub> = nitrogen dioxide; PM<sub>2.5</sub> = particulate matter with an aerodynamic diameter ≤2.5 µm; ROS = reactive oxygen species.



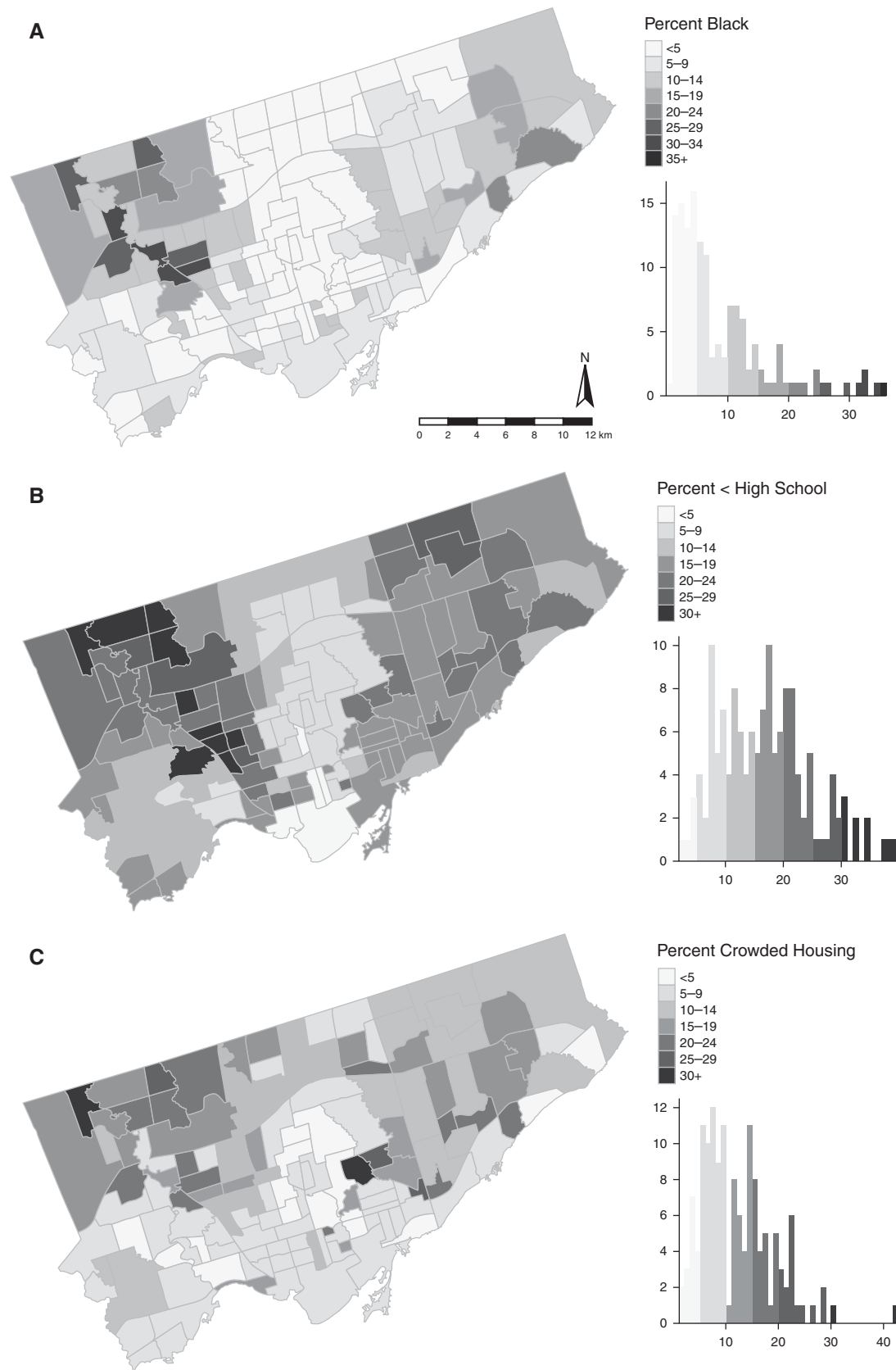
**Figure 1.** Spatial distributions of (A) coronavirus disease (COVID-19) incidence and (B) ROS by neighborhood in Toronto, Canada. ROS = reactive oxygen species.

## Results

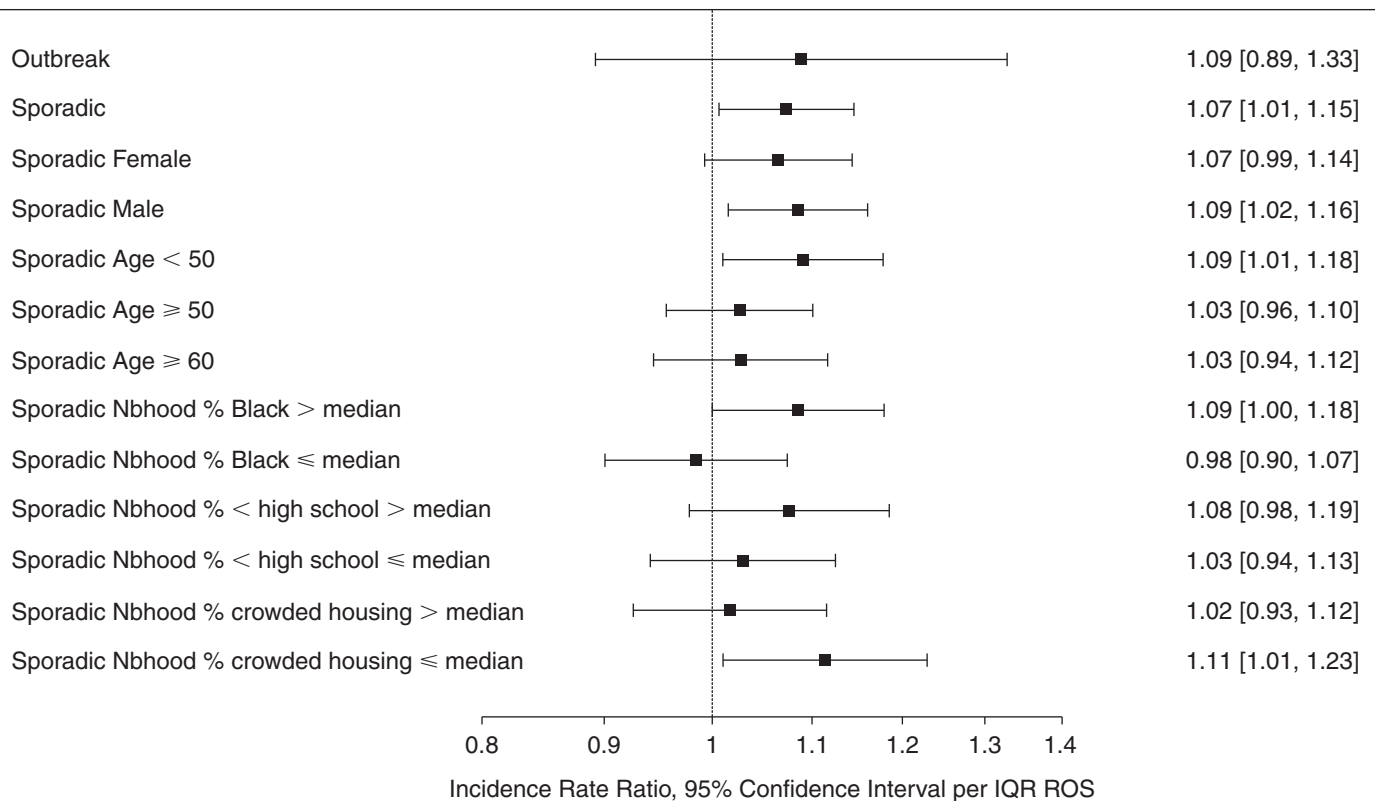
There were 23,061 confirmed cases of COVID-19 in Toronto through October 12, 2020. Of these, 16,415 (71%) were considered sporadic and 6,646 (29%) were considered

outbreak related. Characteristics of cases are summarized in Table 1. The fatality rate was considerably higher for outbreak-related cases than for sporadic cases, whereas the hospitalization rate was only slightly higher. Rates of intensive care admission and

intubation were slightly higher for sporadic cases. Men and women were equally represented among sporadic cases, whereas there was a preponderance of women among outbreak-related cases. The majority of sporadic cases were less than 50 years of age,



**Figure 2.** Spatial distributions of (A) percentage of Black residents, (B) percentage of people with less than a high school education, and (C) percentage of people living in crowded housing by neighborhood in Toronto, Canada.



**Figure 3.** Associations of reactive oxygen species (ROS) with coronavirus disease (COVID-19) incidence by population subgroup based on spatial multivariate models. Incidence rate ratios and their 95% confidence intervals per IQR for ROS are shown. IQR = interquartile range; Nbhood = neighborhood.

whereas the majority of outbreak-related cases were 50 years of age or older.

The distribution of cases, environmental exposures, and sociodemographic characteristics by neighborhood is shown in Table 2 and Figures 1 and 2. High COVID-19 incidence was concentrated in northwest Toronto, together with higher proportions of Black residents and prevalence of crowded housing and less than high school education. ROS concentrations tended to be higher in the southern downtown core as well as northwest Toronto. Spatial variability of exposures at the more highly resolved census dissemination area level is shown for comparison in Figure E2. The highest concentrations of both ROS and NO<sub>2</sub> correspond with locations of major north-south and east-west expressways. They were moderately correlated ( $\rho = 0.51$ ).

Spearman correlations among independent variables are summarized in Figure E3. Strong positive correlations were observed among variables reflecting the prevalence of racialized group membership, nonspeakers of English or French, lower SES, and crowded housing. NO<sub>2</sub> was positively correlated with the prevalence of both less than

high school education and crowded housing, whereas ROS was positively correlated only with the prevalence of crowded housing. The COVID-19 testing rate was strongly negatively correlated with measures of racialized group membership and lower SES, and it was weakly negatively correlated with ROS.

In bivariate analyses of single-exposure variables and COVID-19 incidence, ROS and NO<sub>2</sub> exhibited significant positive associations with COVID-19 incidence, whereas greenness, which was measured by the normalized difference vegetation index (NDVI), exhibited a significant negative association, and PM<sub>2.5</sub> mass exhibited a nonsignificant positive association (see Table E1). However, in joint models simultaneously including ROS and either NO<sub>2</sub> or NDVI, only ROS remained significantly associated with COVID-19 incidence (see Table E2). Several variables representing neighborhood-level racialized group membership and SES exhibited positive associations with COVID-19 incidence. The number of days since first case was significantly negatively associated with COVID-19 incidence, whereas days since peak incidence exhibited a significant positive

association. The 6-week total number of COVID-19 tests was not associated with COVID-19 incidence. In the DAG-based multivariate model (Table 3), ROS, proportion of Black residents, and prevalence of crowded housing and less than high school education remained positively and significantly associated with COVID-19 incidence, whereas days since peak incidence and days since first case exhibited null associations. However, Moran's I indicated that there was significant spatial autocorrelation of the model residuals ( $P < 0.0001$ ), and mapping of residuals indicated that the model tended to overpredict incidence in neighborhoods clustered in northwest Toronto (see Figure E4). A model incorporating neighboring incidence values as a covariate reduced the degree of spatial autocorrelation such that Moran's I was no longer significant ( $P = 0.10$ ) and clustering of residuals was no longer evident (see Figure E4). In this model (Table 3), ROS, proportion of Black residents, and prevalence of crowded housing remained positively and significantly associated with COVID-19 incidence. In subgroup analyses based on the same model (Figure 3), the association of ROS with

**Table 3.** Summary of Regression Models

Variable	IQR	Multivariate		Spatial Multivariate	
		IRR	95% CI	IRR	95% CI
ROS, nmol/L	10.4	1.14	1.06–1.23	1.07	1.01–1.15
Black, %	7.9	1.24	1.14–1.35	1.10	1.01–1.20
Less than high school education, %	10.6	1.19	1.07–1.33	1.05	0.95–1.16
Crowded housing, %	9.0	1.23	1.11–1.35	1.24	1.14–1.35
Days since peak incidence	27.3	1.02	0.99–1.05	1.01	0.98–1.03
Days since first case	12.0	1.00	0.93–1.09	1.02	0.95–1.09

Definition of abbreviations: CI = confidence interval; IQR = interquartile range; IRR = incidence rate ratio; ROS = reactive oxygen species.

outbreak-related cases was less precise than that with sporadic cases ( $P$  for difference = 0.89). ROS was positively and significantly associated with sporadic cases in those less than 50 years of age, whereas associations in other age groups were closer to null ( $P = 0.25$  for difference between <50 yr and  $\geq 50$  yr). A significant positive association was also observed in men ( $P$  for difference vs. women = 0.70). The incidence rate ratio was positive but not significant in neighborhoods with a proportion of Black residents and percentage with less than high school education greater than the median, versus null when at the median or below ( $P$  for difference = 0.11 and 0.51, respectively). The incidence rate ratio was positive and significant for neighborhoods below the median percentage crowded housing and was closer to null for neighborhoods above the median ( $P$  for difference = 0.18).

In other sensitivity analyses (see Table E2), results were not sensitive to employing the 2000–2016 average rather than the 2016 average for  $PM_{2.5}$ ,  $NO_2$ , and NDVI. Associations were also insensitive to the restriction of the analysis to cases before children returned to school, addition of the number of neighborhood COVID-19 tests from August 30 to October 10 as a covariate, specification of days since first case and days since peak incidence as nonlinear terms, and additional or alternative covariates, with the exception that substitution of alternative measures of neighborhood SES resulted in larger magnitude ROS associations and larger model Akaike information criterion values.

## Discussion

To our knowledge, this is the first study to report significant intraurban associations of COVID-19 incidence with estimated generation of ROS in human lung ELF

attributable to metals in  $PM_{2.5}$ . In contrast, we observed a nonsignificant positive association of COVID-19 incidence with  $PM_{2.5}$  mass, which exhibited little spatial variability in the study area. Spatial patterns of ROS in Toronto suggest that it reflects metal-containing PM from sources such as brake wear and railyards (29). In subgroup analyses, ROS was positively and significantly associated with COVID-19 incidence in those less than 50 years of age, whereas associations were closer to null in older age groups. Matz and colleagues (44) reported that adults aged 60 years or more spend significantly more time indoors at home than younger adults as well as significantly less time in vehicles in moderate or heavy traffic or engaged in active transportation in moderate or heavy traffic (45). Differences in associations by age could also be attributable to greater statistical power of the analysis of cases among those younger than 50 years of age, owing to the larger number of cases in this age group. Our finding of a significant association of ROS with COVID-19 incidence for male but not female cases could reflect sex differences in time–activity patterns, in that there is evidence that men spend significantly more time away from home and outdoors than women (44). Differences in time–activity patterns by age and sex are relevant to the likelihood of exposure to both COVID-19 and outdoor air pollution, although time–activity patterns during pandemic restrictions likely differ from those under normal circumstances. Not surprisingly, the association of ROS with outbreak-related cases was considerably less precise than that for sporadic cases, given that outbreak-related cases were older, more likely to be female, and more likely to be resident in institutional settings.

We also found evidence of modification of the association with air pollution by neighborhood proportion of Black residents; a nonsignificant positive association with COVID-19 incidence was observed in

neighborhoods in which the proportion of Black residents was greater than the median, versus null when at the median or below. There have been numerous reports of increased morbidity and mortality from COVID-19 in Black populations (23–26). In an analysis of COVID-19 mortality among 77 Chicago neighborhoods, Kim and colleagues (24) found that COVID-19 deaths, proportion of Black residents, and measures of socioeconomic disadvantage and social vulnerability were clustered in the south and west sides of Chicago, similar to our findings of clustering of cases, racialized group membership, and lower SES in northwest Toronto. Millett and colleagues (25) reported a disproportionate burden of incidence and mortality in counties with a larger proportion of Black residents and, similar to Brandt and colleagues (27), hypothesized that this could be partly mediated by air pollution exposure. Independent of the neighborhood proportion of Black residents, measures of lower SES were also positively associated with COVID-19 incidence in our analysis. This is not surprising, as those with lower income likely have more barriers to self-isolating and social distancing. We also found a nonsignificant positive association of ROS with COVID-19 incidence in neighborhoods in which the percentage of residents with less than a high school education was greater than the median, versus null when at the median or below. Our finding of a significant positive association between ROS and COVID-19 incidence in neighborhoods at or below, but not above, the median percentage living in crowded housing is unexpected. Given the strong association of COVID-19 incidence and neighborhood percentage living in crowded housing, and the clear biological plausibility of this association related to increased opportunity for virus transmission, this finding warrants further evaluation.

In previous studies, Wu and colleagues (22) reported a positive association of long-

term  $PM_{2.5}$  exposure with COVID-19 mortality in an ecological study based on approximately 3,000 U.S. counties. Another study employing similar county-level data reported a significant positive association of  $NO_2$  with COVID-19 mortality and case-fatality rates and a marginally significant positive association between  $PM_{2.5}$  and mortality (19). A Canadian study also reported a positive association of long-term  $PM_{2.5}$  exposure and COVID-19 incidence based on a national analysis of 110 health regions (16). In an analysis conducted in the Netherlands, a significant positive association was observed between  $PM_{2.5}$  and COVID-19 incidence and hospital admissions (17). Colocation of high  $NO_2$  concentrations estimated from remote sensing and high COVID-19 mortality counts in northern Italy and Madrid was reported by Ogen and colleagues (20), but the analysis did not account for important potential confounders, including the underlying population at risk, population density, timing of onset of cases or introduction of control measures, or sociodemographic or health characteristics. Similarly, Frontera and colleagues (18) found that  $PM_{2.5}$  was correlated with COVID-19 incidence, ICU admission, and mortality in Italian regions, but their analysis did not adjust for potential confounders. In the only other study of intraurban associations, Vasquez-Apestequi and colleagues (21) reported that long-term  $PM_{2.5}$  exposure was associated with COVID-19 incidence and mortality in 24 districts in Lima. They accounted for age of onset, sex ratio of cases and deaths, and locations of food markets but not for race/ethnicity or SES. They also employed a relatively coarse spatial resolution (24 districts) and used linear regression, which is not optimal for count data. In time-series analyses based on short-term exposure, significant positive associations were observed between  $PM_{2.5}$ ,  $NO_2$ , and ozone averaged over 2 weeks and COVID-19 incidence in a study in 120 Chinese cities (15), and Adhikari and Yin (14) found that ozone and  $PM_{2.5}$  averaged over 21 days were associated with COVID-19 incidence but not mortality in Queens, New York.

Our study addresses several identified shortcomings of early ecological studies of COVID-19 and air pollution exposure (28) by examining spatial variation in incidence and risk factors at the neighborhood level in a single city where there is likely to be less variability in the nature and timing of public health measures; differentiating between sporadic and outbreak-related cases, the latter

being less plausibly related to outdoor environmental exposures; applying a statistical model (negative binomial) appropriate for count data; accounting for spatial clustering; examining effect modification; and incorporating neighborhood-level testing as a covariate.

Although our study has certain strengths, it also has several limitations. Data on testing were available at the neighborhood level but were not available for the entire time period corresponding with case data. Testing rates were strongly negatively correlated with neighborhood racialized group membership and SES and only weakly negatively correlated with spatial variations in ROS exposures. We conducted analyses within strata of various SES variables and found that the association of ROS with incidence was not sensitive to including weekly testing as a covariate. Data pertaining to changes in mobility in relation to COVID-19 restrictions were not available at the neighborhood level. However, there is evidence based on proprietary mobile phone data from Toronto and elsewhere in Canada and the United States that SES variables included in our analysis are likely to partially reflect differences in these changes by neighborhood, as phone users in census tracts characterized by lower SES reduced their time away from home less than those in higher SES census tracts, potentially owing to fewer opportunities to work remotely in lower wage jobs, considered essential services (46, 47). Nonetheless, residual confounding by factors for which data were not available remains possible. We did have data on population age distribution at the neighborhood level, which would be expected to be strongly correlated with the prevalence of chronic disease and underlying mortality risk. Although we did not have data on smoking prevalence, this is strongly correlated with SES (48), and in our previous analysis smoking prevalence was not associated with COVID-19 incidence at the health region level (16). Nonetheless, like ambient particulate matter, tobacco smoke can also stimulate the production of ROS in ELF (30). Owing to the relatively small sample size, we were not able to include a large number of covariates, opting instead to base the model on a DAG. Strong correlations among covariates, particularly those reflecting racialized group membership and SES, could lead to unstable regression coefficients, but this was not observed in the final multivariate model or sensitivity analyses. ROS exposure estimates were based on observations over a single year; however, there is evidence of

temporal stability in spatial patterns of other pollutants with traffic sources (49, 50), and, in most neighborhoods, the majority of residents had not moved in the previous 5 years. In addition, the ROS exposure estimates likely underestimate the overall impact of air pollution on ROS generation and imprecisely reflect spatial variation, as they do not account for ROS generation from other redox-active PM components such as quinones and organic hydroperoxides nor all biological responses that may lead to release of ROS (29). Finally, although our analysis is based on intraurban rather than interregion variability, both air pollution exposures and sociodemographic characteristics likely vary at smaller scales, and, as this is an ecological study, it should not be used to infer causality at the individual level. However, pending future analyses based on individual-level data, we believe there is public health value in identifying neighborhood characteristics (and interactions among these characteristics) that are associated with increased incidence of COVID-19, particularly where this highlights potential inequality and when interventions can be made on a neighborhood level.

Future ecological studies of intraurban determinants of COVID-19 incidence and mortality should endeavor to employ air pollution measures reflective of specific sources and mechanisms and include intraurban data on mobility patterns during COVID-19 restrictions and access to testing as covariates to address concerns about residual confounding by these factors. To facilitate these analyses, holders of COVID-19 case data should be encouraged to make the data available at the highest possible spatial resolution permitted by privacy guidelines, in a timely fashion, with wide geographic coverage over multiple centers, employing nationally consistent methodology. We acknowledge, however, that some data, such as proprietary mobility data, may be costly, particularly at high spatial resolution, and that COVID-19 data holders, particularly in low-income countries, may lack the resources to provide high-resolution data.

## Conclusions

On the basis of an analysis of 140 neighborhoods in Toronto, Canada, we found that estimated generation of ROS in the human lung attributable to  $PM_{2.5}$  was significantly associated with COVID-19 incidence, and there was evidence of effect modification by racialized group



membership and SES. Although these findings are insufficient to conclude that fine particulate-related oxidative stress is causally related to COVID-19 incidence, the examination of neighborhood characteristics associated with COVID-19 incidence can serve to identify potential inequalities and generate hypotheses for

future studies once individual-level data are available. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

**Acknowledgment:** The authors thank Liz Corson (Toronto Public Health) for advice and

facilitation of data access, Phil Blagden and Keith Van Ryswyk (Health Canada) for helpful comments on the manuscript, and Marc Smith-Doiron (Health Canada) for assistance in mapping air pollution data. Fine particulate matter, NO<sub>2</sub>, and normalized difference vegetation index metrics indexed to DMTI Spatial Inc. postal codes were provided by the Canadian Urban Environmental Health Research Consortium.

## References

- Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, *et al*. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J* 2017;49:1600419.
- Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM<sub>2.5</sub> and daily mortality and hospital admissions: a systematic review and meta-analysis. *Thorax* 2014;69:660–665.
- Domingo JL, Rovira J. Effects of air pollutants on the transmission and severity of respiratory viral infections. *Environ Res* 2020;187:109650.
- Nhung NTT, Amini H, Schindler C, Kutlar Joss M, Dien TM, Probst-Hensch N, *et al*. Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies. *Environ Pollut* 2017;230:1000–1008.
- Mehta S, Shin H, Burnett R, North T, Cohen AJ. Ambient particulate air pollution and acute lower respiratory infections: a systematic review and implications for estimating the global burden of disease. *Air Qual Atmos Health* 2013;6:69–83.
- Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med* 2010;181:47–53.
- Yang L, Li C, Tang X. The impact of PM<sub>2.5</sub> on the host defense of respiratory system. *Front Cell Dev Biol* 2020;8:91.
- Glencross DA, Ho T-R, Camiña N, Hawrylowicz CM, Pfeffer PE. Air pollution and its effects on the immune system. *Free Radic Biol Med* 2020;151:56–68.
- Gao D, Ripley S, Weichenthal S, Godri Pollitt KJ. Ambient particulate matter oxidative potential: Chemical determinants, associated health effects, and strategies for risk management. *Free Radic Biol Med* 2020;151:7–25.
- Ciencewicki J, Jaspers I. Air pollution and respiratory viral infection. *Inhal Toxicol* 2007;19:1135–1146.
- Cai Q-C, Lu J, Xu Q-F, Guo Q, Xu D-Z, Sun Q-W, *et al*. Influence of meteorological factors and air pollution on the outbreak of severe acute respiratory syndrome. *Public Health* 2007;121:258–265.
- Kan H-D, Chen B-H, Fu C-W, Yu S-Z, Mu L-N. Relationship between ambient air pollution and daily mortality of SARS in Beijing. *Biomed Environ Sci* 2005;18:1–4.
- Cui Y, Zhang Z-F, Froines J, Zhao J, Wang H, Yu S-Z, *et al*. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. *Environ Health* 2003;2:15.
- Adhikari A, Yin J. Short-term effects of ambient ozone, PM<sub>2.5</sub>, and meteorological factors on COVID-19 confirmed cases and deaths in Queens, New York. *Int J Environ Res Public Health* 2020;17:4047.
- Zhu Y, Xie J, Huang F, Cao L. Association between short-term exposure to air pollution and COVID-19 infection: Evidence from China. *Sci Total Environ* 2020;727:138704.
- Stieb DM, Evans GJ, To TM, Brook JR, Burnett RT. An ecological analysis of long-term exposure to PM<sub>2.5</sub> and incidence of COVID-19 in Canadian health regions. *Environ Res* 2020;191:110052.
- Andree BPJ. Incidence of COVID-19 and connections with air pollution exposure: evidence from the Netherlands. *medRxiv* [preprint]. 2020. Available from <https://www.medrxiv.org/content/10.1101/2020.04.27.20081562v1>.
- Frontera A, Cianfanelli L, Vlachos K, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: The “double-hit” hypothesis. *J Infect* 2020;81:255–259.
- Liang D, Shi L, Zhao J, Liu P, Sarnat JA, Gao S, *et al*. Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. *Innovation (N Y)* 2020;1:100047.
- Ogen Y. Assessing nitrogen dioxide (NO<sub>2</sub>) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci Total Environ* 2020;726:138605.
- Vasquez-Apestegui V, Parras-Garrido E, Tapia V, Paz-Aparicio VM, Rojas JP, Sánchez-Ccoyllo OR, *et al*. Association between air pollution in Lima and the high incidence of COVID-19: findings from a post hoc analysis. *Research Square* [preprint]. 2020. Available from <https://www.researchsquare.com/article/rs-39404/v1>.
- Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis. *Sci Adv* 2020;6:eabd4049.
- Dyer O. Covid-19: Black people and other minorities are hardest hit in US. *BMJ* 2020;369:m1483.
- Kim SJ, Bostwick W. Social vulnerability and racial inequality in COVID-19 deaths in Chicago. *Health Educ Behav* 2020;47:509–513.
- Millett GA, Jones AT, Benkeser D, Baral S, Mercer L, Beyrer C, *et al*. Assessing differential impacts of COVID-19 on black communities. *Ann Epidemiol* 2020;47:37–44.
- Yancy CW. COVID-19 and African Americans. *JAMA* 2020;323:1891–1892.
- Brandt EB, Beck AF, Mersha TB. Air pollution, racial disparities, and COVID-19 mortality. *J Allergy Clin Immunol* 2020;146:61–63.
- Villeneuve PJ, Goldberg MS. Methodological considerations for epidemiological studies of air pollution and the SARS and COVID-19 coronavirus outbreaks. *Environ Health Perspect* 2020;128:95001.
- Weichenthal S, Shekarrizfard M, Kulka R, Lakey PSJ, Al-Rijeh K, Anowar S, *et al*. Spatial variations in the estimated production of reactive oxygen species in the epithelial lung lining fluid by iron and copper in fine particulate air pollution. *Environ Epidemiol* 2018;2:e020.
- Lakey PSJ, Berkemeier T, Tong H, Arangio AM, Lucas K, Pöschl U, *et al*. Chemical exposure-response relationship between air pollutants and reactive oxygen species in the human respiratory tract. *Sci Rep* 2016;6:32916.
- City of Toronto. COVID-19 cases in Toronto. 2020 [accessed 2020 Oct 13]. Available from: <https://open.toronto.ca/dataset/covid-19-cases-in-toronto/>.
- R Core Team. R: A language and environment for statistical computing. 2019 [accessed 2020 Sep 1]. Available from: <https://www.R-project.org/>.
- Brunsdon C, Chen H. GISTools: Some further GIS capabilities for R. R package version 0.7-4. 2014 [accessed 2020 Sep 1]. Available from: <https://CRAN.R-project.org/package=GISTools>.
- Bivand R, Kitt T, Rowlington B. rgdal: bindings for the “Geospatial” Data Abstraction Library. R package version 1.4-8. 2019 [accessed 2020 Sep 1]. Available from: <https://CRAN.R-project.org/package=rgdal>.
- Hijmans R. raster: geographic data analysis and modeling. R package version 3.0-12. 2020 [accessed 2020 Sep 1]. Available from: <https://CRAN.R-project.org/package=raster>.
- Adams ML, Katz DL, Grandpre J. Population-based estimates of chronic conditions affecting risk for complications from coronavirus disease, United States. *Emerg Infect Dis* 2020;26:1831–1833.
- City of Toronto. Neighbourhood profiles. 2019 [accessed 2020 Sep 1]. Available from: <https://open.toronto.ca/dataset/neighbourhood-profiles/>.
- Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package ‘dagitty.’ *Int J Epidemiol* 2017;45:1887–1894.
- Bivand R, Wong D. Comparing implementations of global and local indicators of spatial association. *TEST* 2018;27:716–748.
- Bivand R, Pebesma E, Gomez-Rubio V. Applied spatial data analysis with R. New York, NY: Springer; 2013.

41. Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015;67:1–48.
42. Venables W, Ripley B. *Modern applied statistics with S*. New York, NY: Springer; 2002.
43. Wood S. *Generalized additive models: an introduction with R*, 2nd ed. London, UK: Chapman and Hall/CRC; 2017.
44. Matz CJ, Stieb DM, Davis K, Egyed M, Rose A, Chou B, *et al*. Effects of age, season, gender and urban-rural status on time-activity: Canadian Human Activity Pattern Survey 2 (CHAPS 2). *Int J Environ Res Public Health* 2014;11:2108–2124.
45. Matz CJ, Stieb DM, Egyed M, Brion O, Johnson M. Evaluation of daily time spent in transportation and traffic-influenced microenvironments by urban Canadians. *Air Qual Atmos Health* 2018;11:209–220.
46. Environics Analytics. Are we listening? A view into Americans' compliance with COVID-19 movement restrictions. 2020 [accessed 2020 Oct 23]. Available from: <https://www.prnswire.com/news-releases/are-we-listening-a-view-into-americans-compliance-with-covid-19-movement-restrictions-301051095.html>.
47. Seoni R. Are we listening? A view into Canadians' compliance with COVID-19 movement restrictions. Environics Analytics; 2020.
48. Smith P, Frank J, Mustard C. Trends in educational inequalities in smoking and physical activity in Canada: 1974-2005. *J Epidemiol Community Health* 2009;63:317–323.
49. Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K, *et al*. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health* 2012;11:48.
50. Eeftens M, Beelen R, Fischer P, Brunekreef B, Meliefste K, Hoek G. Stability of measured and modelled spatial contrasts in NO<sub>2</sub> over time. *Occup Environ Med* 2011;68:765–770.