Research

Association between long-term exposure to ambient air pollution and COVID-19 severity: a prospective cohort study

Chen Chen PhD, John Wang MS, Jeff Kwong MD, JinHee Kim MD, Aaron van Donkelaar PhD, Randall V. Martin PhD, Perry Hystad PhD, Yushan Su PhD, Eric Lavigne PhD, Megan Kirby-McGregor MS, Jay S. Kaufman PhD, Tarik Benmarhnia PhD, Hong Chen PhD

Cite as: *CMAJ* 2022 May 24;194:E693-700. doi: 10.1503/cmaj.220068

Abstract

Background: The tremendous global health burden related to COVID-19 means that identifying determinants of COVID-19 severity is important for prevention and intervention. We aimed to explore long-term exposure to ambient air pollution as a potential contributor to COVID-19 severity, given its known impact on the respiratory system.

Methods: We used a cohort of all people with confirmed SARS-CoV-2 infection, aged 20 years and older and not residing in a long-term care facility in Ontario, Canada, during 2020. We evaluated the association between long-term exposure to fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and ground-level ozone (O_3), and risk of COVID-19-related hospital admission, intensive care unit (ICU) admission and death. We ascertained individuals' long-term exposures to each air pollutant based on their residence from 2015 to 2019. We used logistic regression and adjusted for confounders and selection bias using various individual and contextual covariates obtained through data linkage.

Results: Among the 151 105 people with confirmed SARS-CoV-2 infection in Ontario in 2020, we observed 8630 hospital admissions, 1912 ICU admissions and 2137 deaths related to COVID-19. For each interquartile range increase in exposure to $PM_{2.5}$ (1.70 μg/m^3), we estimated odds ratios of 1.06 (95% confidence interval [CI] 1.01–1.12), 1.09 (95% CI 0.98–1.21) and 1.00 (95% CI 0.90–1.11) for hospital admission, ICU admission and death, respectively. Estimates were smaller for NO_2. We also estimated odds ratios of 1.15 (95% CI 1.06–1.23), 1.30 (95% CI 1.12–1.50) and 1.18 (95% CI 1.02–1.36) per interquartile range increase of 5.14 ppb in O_3 for hospital admission, ICU admission and death, respectively.

Interpretation: Chronic exposure to air pollution may contribute to severe outcomes after SARS-CoV-2 infection, particularly exposure to O_3.

By November 2021, COVID-19 had caused more than 5 million deaths globally[1] and more than 29 400 in Canada.[2] The clinical manifestations of SARS-CoV-2 infection range from being asymptomatic to multiple organ failure and death. Identifying risk factors for COVID-19 severity is important to better understand etiological mechanisms and identify populations to prioritize for screening, vaccination and medical treatment. Risk factors for severity of COVID-19 include male sex, older age, pre-existing medical conditions and being from racialized communities.[3–5] More recently, ambient air pollution has been implicated as a potential driver of COVID-19 severity.[6–10]

Long-term exposure to ambient air pollution, a major contributor to global disease burden,[11] could increase the risk of severe COVID-19 outcomes by several mechanisms. Air pollutants can reduce individuals' pulmonary immune responses and antimicrobial activities, boosting viral loads.[8] Air pollution can also induce chronic inflammation and overexpression of the alveolar angiotensin-converting enzyme 2 (ACE) receptor,[7] the key receptor that facilitates SARS-CoV-2 entry into cells.[12,13] Exposure to air pollution contributes to chronic conditions, such as cardiovascular disease, that are associated with unfavourable COVID-19 prognosis, possibly owing to persistent immune activation and excessive amplification of cytokine development.[10] Thus, greater exposure to long-term air pollution may lead to severe COVID-19 outcomes.

Reports exist of positive associations between long-term exposure to particulate matter with diameters equal to or smaller than 2.5 or 10 μm ($PM_{2.5}$ and PM_{10}), ground-level ozone (O_3) and nitrogen dioxide (NO_2), and metrics of COVID-19 severity

© 2022 CMA Impact Inc. or its licensors

(e.g., mortality and case fatality rate).[8–10] However, most studies to date have used ecological and cross-sectional designs, owing to limited access to individual data, which leads to ambiguity in interpreting the results, thus hindering their influence on policy.[6,14] Ecological designs do not allow for disentangling the relative impacts of air pollution on individual susceptibility to infection and disease severity.[14] Residual confounding by factors such as population mobility and social interactions is also problematic. Therefore, a cohort study with data on individuals with SARS-CoV-2 is a more appropriate design.[6,14] Studies that have used individual data were conducted in specific subpopulations[15,16] or populations with few severe cases,[17] or had limited data on individual exposure to air pollutants.[18] In Canada, 1 ecological study found a positive association between long-term exposure to $PM_{2.5}$ and COVID-19 incidence,[19] but no published study has explored the association between air pollution and COVID-19 severity.

We aimed to examine the associations between long-term exposure to 3 common air pollutants ($PM_{2.5}$, NO_2 and O_3) and key indicators of COVID-19 severity, including hospital admission, intensive care unit (ICU) admission and death, using a large prospective cohort of people with confirmed SARS-CoV-2 infection in Ontario, Canada, in 2020. The air contaminants $PM_{2.5}$, NO_2 and O_3 are regularly monitored by the Canadian government, and are key pollutants that are considered when setting air-quality policies. They originate from varying sources (NO_2 is primarily emitted during combustion of fuel, O_3 is primarily formed in air by chemical reactions of nitrogen oxides and volatile organic compounds, and $PM_{2.5}$ can be emitted during combustion or formed by reactions of chemicals like sulphur dioxide and nitrogen oxides in air) and they may affect human health differently.[20,21,22]

Methods

Study population and data sources

We constructed a population-based cohort comprising all people with confirmed SARS-CoV-2 infection aged 20 years or older and who did not reside in a long-term care facility in Ontario, Canada, throughout 2020. We excluded residents of long-term care facilities, given that their profile of frailty and air pollution exposure differs from that of the general population. We used data from Ontario's Case and Contact Management System and the Ontario Laboratories Information System, which recorded specimen collection date (date of diagnosis), demographics and socioeconomic status of people with SARS-CoV-2 infection, as well as the incidence of COVID-19–related hospital admission, ICU admission and death.[23,24] We followed up outcomes until their occurrence or May 2021, whichever came first.

Covariates and exposures

We obtained information on key factors that might confound the association between air pollution and COVID-19 severity (detailed list of data sources in Appendix 1, eTable 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.220068/tab-related-content). Briefly, we obtained data on health care access and pre-existing conditions of individuals, using hospital discharge data from the Canadian Institute for Health Information Discharge Abstract Database and physician service claims in the Ontario Health Insurance Plan database. We linked the cohort to Ontario's Registered Persons Database, a registry of all Ontario residents with a health insurance number, to obtain individuals' annual residential address over the 5 years before 2020. We also obtained their neighbourhood-level socioeconomic status through linkage with Census data; details are described elsewhere.[25] We used annual exposure surfaces of $PM_{2.5}$, NO_2 and O_3 developed previously, which showed good performance in evaluations: the $PM_{2.5}$ surface exhibited $R^2 = 0.73$ in long-term cross-validation with measurements;[26] the NO_2 model accounted for 73% of the variability in annual measurements;[27] and the O_3 model's proportion of correct predicted values ranged from 65% to 93%, depending on the time of day[28] (Appendix 1, Section 1). Using these surfaces and individuals' annual residential address, we calculated their long-term exposures to air pollutants as the average postal code–specific annual concentrations at their residential addresses in the 5 years before the pandemic (2015 to 2019).

Statistical analysis

Data sets were linked using unique encoded identifiers and analyzed at ICES. We applied multivariable logistic regression models to investigate the associations between long-term exposure to 3 ambient air pollutants ($PM_{2.5}$, O_3 and NO_2) and 3 indicators of severity of COVID-19 (COVID-19–related hospital admission, ICU admission and death) separately after assessing relevant assumptions. We estimated odds ratios (ORs) to approximate risk ratios because these 3 outcomes were relatively rare. In this study, we focused on cumulative incidence of the outcomes over the entire follow-up period.

Because uncertainty exists regarding the mechanisms of how long-term exposure to air pollution might affect COVID-19 severity and data availability varies across studies, it has been suggested that different variables should be controlled for to reduce confounding in observational studies of COVID-19 severity.[14,16,29] We applied the "disjunctive cause criterion," which includes any pre-exposure covariate that is a cause of the exposure or the outcome, or both.[30] Additionally, we adjusted for contextual factors that correlate with air pollution and may also affect the probability of testing for SARS-CoV-2 in an attempt to account for selection bias.[31] This is because inclusion in the study cohort required that a person test positive for SARS-CoV-2 infection, which is affected by the severity of symptoms, thus creating a collider between exposure and outcome (see Appendix 1, eFigure 1 for a directed acyclic graph depicting this possible selection bias).[32] Using literature on air pollution and health in Canada,[33,34] evidence about the drivers of COVID-19 severity[3–5,16] and recently identified contextual factors associated with testing positive for SARS-CoV-2 infection in Ontario,[35] we considered 5 sequential models with different sets of covariates (model specifications in Appendix 1, Section 2), with Model 5 as the full model (see Appendix 1, eFigure 2 for the directed acyclic graph). Briefly, we adjusted for date of

diagnosis, demographics (sex and age), being part of an outbreak, being an essential worker, neighbourhood income, health care access (number of outpatient visits in 2019, influenza vaccination status and distance to nearest health services), neighbourhood socioeconomic status (average household size and the Ontario Marginalization Index), and other contextual factors (rurality, population density and health regions). Because the Ontario Marginalization Index encompasses 4 dimensions of socioeconomic status using dissemination area–level Census data, we excluded Census variables that are included in the Ontario Marginalization Index, to avoid multicollinearity.[36] The same set of models was applied for all combinations of exposure and outcome.

We conducted sensitivity analyses (see details in Appendix 1, Section 3) considering 10 alternative models in which we explored additional sets of covariates and different exposure windows. We also evaluated whether the exposure–outcome association departed from linearity using restricted cubic spline, estimated the controlled direct effect by further adjusting for pre-existing conditions, excluded events that occurred more than 90 days after initial diagnosis, restricted to events that occurred after May 24, 2020 (when testing became available to asymptomatic people),[37] and excluded people with extreme exposures (> 99% or < 1%). We conducted all analyses using SAS (EG 7.11).

Ethics approval

Use of ICES data in this study was authorized under section 45 of the *Personal Health Information Protection Act* of Ontario, which does not require review by a Research Ethics Board.

Results

Among 151 105 people recorded as being infected with SARS-CoV-2 in Ontario in 2020 (Figure 1), we identified 8630 (5.7%), 1912 (1.3%) and 2137 (1.4%) COVID-19–related hospital admissions, ICU admissions and deaths, respectively. The median times between first diagnosis and hospital admission, ICU admission and death were 5 days, 8 days and 15 days, respectively. The medians (interquartile ranges [IQRs]) of long-term exposure to air pollutants were 7.64 μg/m^3 (6.43–8.13), 7.75 ppb (6.15–8.65) and 44.80 ppb (42.41–47.38) for $PM_{2.5}$, NO_2 and O_3, respectively. Cohort characteristics are summarized by outcome in Table 1 and by exposure in Appendix 1, eTable 2.

Higher exposure to $PM_{2.5}$ was associated with an increased risk of both hospital and ICU admission in Models 1 to 3 (Appendix 1, eFigure 3). Adjustment for neighbourhood socioeconomic status attenuated the associations toward the null. In the final model adjusting for additional contextual factors (Figure 2), we obtained ORs of 1.06 (95% confidence interval [CI] 1.01–1.12) and 1.09 (95% CI 0.98–1.21) per IQR increase of 1.70 μg/m^3 for hospital admission and ICU admission, respectively (Appendix 1, eTable 4). Although death was positively associated with $PM_{2.5}$ in Models 1 to 4, we did not observe an effect in the fully adjusted model (OR 1.00 [95% CI 0.90–1.11]).

For NO_2, we found similar patterns in results of sequential models (1–4) as for $PM_{2.5}$. In the fully adjusted model, we obtained ORs of 1.09 (95% CI 0.97–1.21) per IQR increase of 2.50 ppb NO_2 for ICU admission, while we did not observe an effect for hospital admission (OR 1.01 [95% CI 0.95–1.07]) or death (OR 1.02 [95% CI 0.91–1.15]).

For O_3, we found no evidence for an association in the partially adjusted models (Models 1–4). In the fully adjusted model,

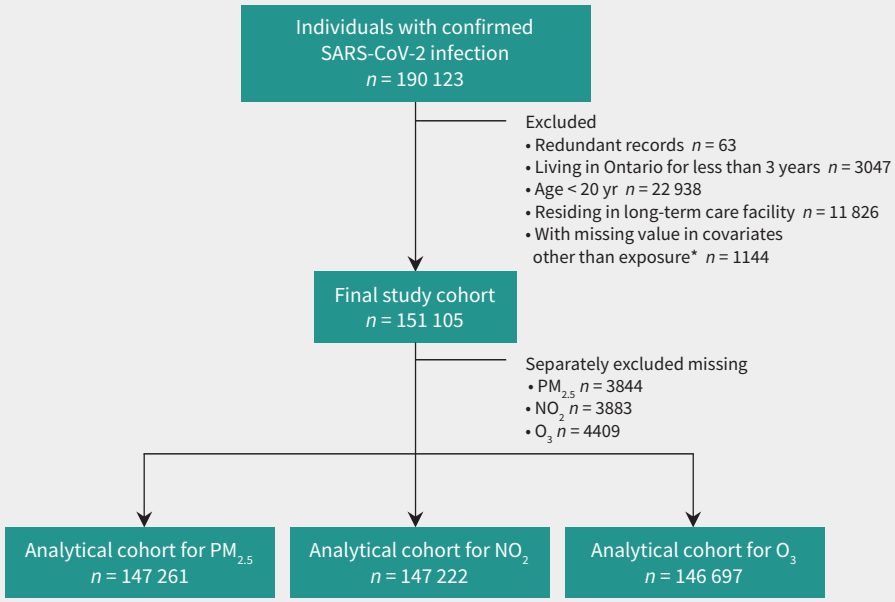

Figure 1: Flow chart showing the creation of the cohort. Note: *Based on covariates included in the final model (Model 5).

Table 1 (part 1 of 2): Demographics, socioeconomic status, health behaviour and characteristics of infection in study cohort (all adults with SARS-CoV-2 infection in Ontario, Canada, in 2020) and in subcohorts experiencing COVID-19–related outcomes

Characteristic	No. (%)* of people in entire cohort *n* = 151 105	No. (%)* of people admitted to hospital *n* = 8630	No. (%)* of people admitted to ICU *n* = 1912	No. (%)* of people who died *n* = 2137
Demographics				
Male	74 043 (49.0)	4827 (55.9)	1258 (65.8)	1268 (59.3)
Age, yr, median (IQR)	44 (31–57)	69 (56–81)	65 (56–74)	80 (71–88)
Characteristics of SARS-CoV-2 infection				
Outbreak-related†	26 382 (17.5)	2032 (23.5)	249 (13.0)	851 (39.8)
Essential worker‡	22 441 (14.9)	492 (5.7)	115 (6.0)	31 (1.50%)
Socioeconomic status				
Neighbourhood income in 2016				
1st quintile (lowest)	36 695 (24.3)	2611 (30.3)	559 (29.2)	628 (29.4)
2nd quintile	33 363 (22.1)	1978 (22.9)	459 (24.0)	503 (23.5)
3rd quintile	33 002 (21.8)	1664 (19.3)	369 (19.3)	432 (20.2)
4th quintile	26 555 (17.6)	1300 (15.1)	291 (15.2)	307 (14.4)
5th quintile (highest)	21 490 (14.2)	1077 (12.5)	234 (12.2)	267 (12.5)
Health care access				
No. of outpatient visits in 2019, median (IQR)	2 (1–5)	6 (2–11)	5 (2–10)	7 (3–12)
Influenza vaccination	27 876 (18.4)	2928 (33.9)	661 (34.6)	887 (41.5)
Normalized distance to nearest health services, mean ± SD§	0.02 ± 0.04	0.03 ± 0.05	0.02 ± 0.04	0.03 ± 0.04
Neighbourhood-level (dissemination area) socioeconomic status				
Average household size, median (IQR)	3 (3)	3 (2–3)	3 (2–3)	3 (2–3)
Ontario Marginalization Index: ethnic concentration				
1st quintile (lowest)	8904 (5.9)	623 (7.2)	114 (6.0)	176 (8.2)
2nd quintile	13 289 (8.8)	866 (10.0)	191 (10.0)	285 (13.3)
3rd quintile	19 572 (12.9)	1219 (14.1)	273 (14.3)	360 (16.8)
4th quintile	31 936 (21.1)	1936 (22.4)	422 (22.1)	478 (22.4)
5th quintile (highest)	77 404 (51.2)	3986 (46.2)	912 (47.7)	838 (39.2)
Ontario Marginalization Index: residential instability				
1st quintile (lowest)	42 724 (28.2)	1720 (19.9)	410 (21.4)	315 (14.7)
2nd quintile	25 362 (16.8)	1267 (14.7)	311 (16.3)	312 (14.6)
3rd quintile	23 172 (15.3)	1281 (14.8)	317 (16.6)	347 (16.2)
4th quintile	24 028 (15.9)	1583 (18.3)	347 (18.1)	381 (17.8)
5th quintile (highest)	35 819 (23.7)	2779 (32.2)	527 (27.6)	782 (36.6)
Ontario Marginalization Index: material deprivation				
1st quintile (lowest)	25 642 (17.0)	1313 (15.2)	263 (13.8)	335 (15.7)
2nd quintile	26 421 (17.5)	1368 (15.9)	267 (14.0)	365 (17.1)
3rd quintile	29 948 (19.8)	1599 (18.5)	381 (19.9)	403 (18.9)
4th quintile	31 872 (21.1)	1844 (21.4)	426 (22.3)	453 (21.2)
5th quintile (highest)	37 222 (24.6)	2506 (29.0)	575 (30.1)	581 (27.2)

Table 1 (part 2 of 2): Demographics, socioeconomic status, health behaviour and characteristics of infection in study cohort (all adults with SARS-CoV-2 infection in Ontario, Canada, in 2020) and in subcohorts experiencing COVID-19–related outcomes

Characteristic	No. (%)* of people in entire cohort *n* = 151 105	No. (%)* of people admitted to hospital *n* = 8630	No. (%)* of people admitted to ICU *n* = 1912	No. (%)* of people who died *n* = 2137
Ontario Marginalization Index: dependency				
1st quintile (lowest)	52 603 (34.8)	2214 (25.7)	509 (26.6)	384 (18.0)
2nd quintile	34 309 (22.7)	1812 (21.0)	426 (22.3)	376 (17.6)
3rd quintile	25 055 (16.6)	1477 (17.1)	348 (18.2)	364 (17.0)
4th quintile	20 955 (13.9)	1411 (16.3)	333 (17.4)	430 (20.1)
5th quintile (highest)	18 183 (12.0)	1716 (19.9)	296 (15.5)	583 (27.3)
Other contextual factors for spatial heterogeneity in quality of care				
Rural area¶	2887 (1.9)	175 (2.0)	44 (2.3)	36 (1.7)
Neighbourhood-level population density per km^2, median (IQR)	3886 (1904–7002)	4075 (2050–7793)	3986 (2000–7407)	3744 (1957–7601)
Health region unique** ID				
2253	35 587 (23.6)	1244 (14.4)	232 (12.1)	238 (11.1)
2270	16 347 (10.8)	842 (9.8)	173 (9.0)	232 (10.9)
3501	8593 (5.7)	397 (4.6)	66 (3.5)	123 (5.8)
3502	5056 (3.3)	382 (4.4)	92 (4.8)	128 (6.0)
3503	6632 (4.4)	414 (4.8)	112 (5.9)	90 (4.2)
3504	11 211 (7.4)	750 (8.7)	170 (8.9)	205 (9.6)
3505	938 (0.6)	44 (0.5)	7 (0.4)	10 (0.5)
3509	6912 (4.6)	386 (4.5)	101 (5.3)	81 (3.8)
3510	939 (0.6)	67 (0.8)	14 (0.7)	15 (0.7)
3511	8327 (5.5)	527 (6.1)	116 (6.1)	118 (5.5)
3512	1966 (1.3)	141 (1.6)	30 (1.6)	32 (1.5)
3513	552 (0.4)	49 (0.6)	18 (0.9)	13 (0.6)
3514	526 (0.3)	31 (0.4)	9 (0.5)	≤ 5 (0.1)
3895	47 519 (31.4)	3356 (38.9)	772 (40.4)	849 (39.7)

Note: ICU = intensive care unit, IQR = interquartile range, SD = standard deviation.
*Unless otherwise specified.
†We define an infection as outbreak-related if it is linked to a declared outbreak of SARS-CoV-2 infection. This field represents all outbreaks, as determined by the local public health unit, and is not limited to outbreaks in any particular setting.
‡We define individuals as essential workers if they satisfy any of the following criteria: work in an adult or youth addiction setting, work in an adult developmental services residential setting, work as animal or animal product handlers, work in violence against women or anti–human trafficking residential site, work in children's residential setting, work in another type of congregate care setting not specifically listed, work in correctional facility, provide custodial services, work as dental hygienists, work as doctors, work as educational staff, work as farm workers, work as first responders, work as grocery workers, work as health care workers, work as shelter staff or homeless workers, work in a hospital, work in long-term care home, work as laboratory workers with infectious agents and materials, work as medical technicians in a clinic or hospital setting, work as midwife, work in a mine, work on a mink farm, work as municipal workers, work as nurses, work as personal support workers, work as respiratory therapists, work in a retirement home, work as rotational worker, work as veterinarians, work in a child-care centre or in a type of supportive housing.
§We define distance to nearest health services as the distances of a dissemination block to any dissemination block with a health care facility. The original distance was normalized.
¶We define rural as communities with a rurality index of Ontario (2008 version) > 40, which considers population and travel time to referral centres.
**We define health region as a combination of Ontario Local Health Integration Networks and public health unit. The following general regions correspond to each health region unique ID: 2253-York region, 2279-Peel region, 3501-Erie St. Clair region, 3502-South West region, 3503-Waterloo Wellington region, 3504-Hamilton Niagara Haldimand Brant region, 3505-Central West region, 3509-Central East region, 3510-South East region, 3511-Champlain region, 3512-North Simcoe Muskoka region, 3513-North East region, 3514-North West region, 3895-Toronto region.

O_3 exposure was associated with an increased risk for all 3 outcomes, with ORs of 1.15 (95% CI 1.06–1.23), 1.30 (95% CI 1.12–1.50) and 1.18 (95% CI 1.02–1.36) per IQR increase of 5.14 ppb for hospital admission, ICU admission and death, respectively.

In sensitivity analyses, we found estimates similar to those of the main model when adjusting for additional covariates, using different exposure windows, restricting to events that occurred within 90 days of diagnosis (enrolment date), excluding people with extreme exposures, and accounting for the effect mediated through pre-existing

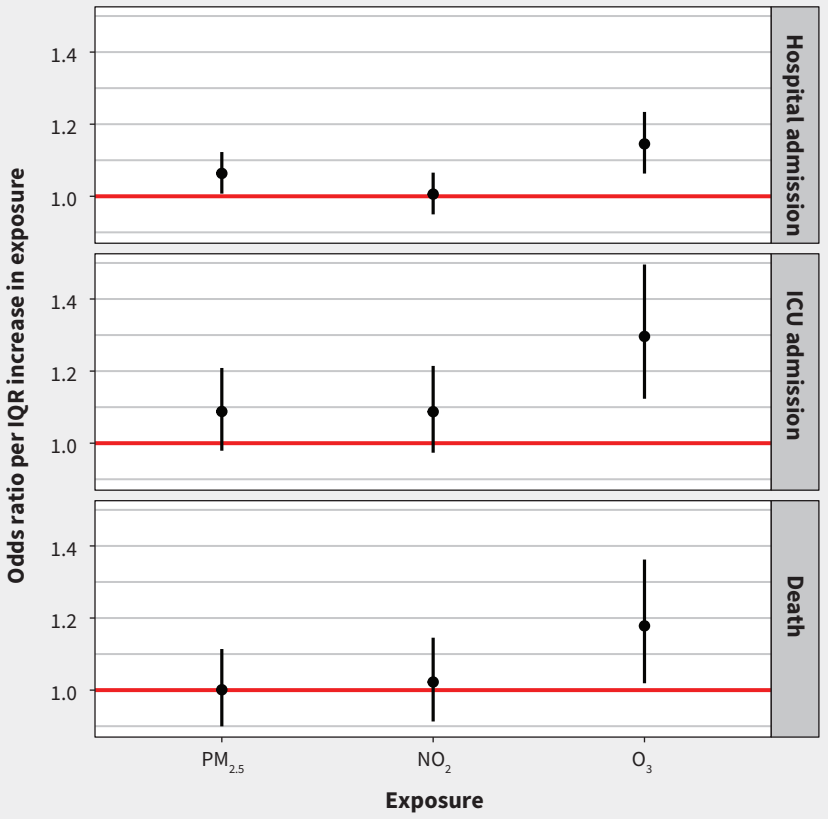

Figure 2: Association between average exposure to air pollutants and severe outcomes of SARS-CoV-2 infection in odds ratio per interquartile range (IQR)* increase in exposure for the final model (Model 5). Note: ICU = intensive care unit. *Interquartile range represents the difference between 75th and 25th percentile of the exposure.

conditions caused by air pollution (Appendix 1, eFigure 4). The associations increased for O_3 but attenuated for NO_2 and $PM_{2.5}$ in the period after May 24 (Appendix 1, Section 3). We observed no evidence of departure from linearity for the air pollutant–outcome associations based on likelihood ratio tests.

Interpretation

We observed that people with SARS-CoV-2 infection who lived in areas of Ontario with higher levels of common air pollutants ($PM_{2.5}$, NO_2 and O_3) were at elevated risk of being admitted to the ICU after we adjusted for individual and contextual confounding factors, even when the air pollution level was relatively low. In addition, we found that chronic exposure to $PM_{2.5}$ and O_3 was associated with elevated risk of COVID-19–related hospital admission, and exposure to O_3 was also associated with elevated risk of death due to COVID-19. These results suggest that chronic exposure to air pollution before SARS-CoV-2 infection may contribute to COVID-19 severity, particularly chronic exposure to O_3.

Previous ecological studies found positive associations between long-term exposure to $PM_{2.5}$, NO_2 and O_3, and COVID-19 mortality and case fatality rate.[29,38,39] In other, more limited, cohort studies, Bowe and colleagues found a relative risk of 1.09 (95% CI 1.07–1.11) per 1.70 μg/m^3 increase in $PM_{2.5}$ concentration for hospital admission among American veterans who received a diagnosis of COVID-19,[16] while Bozack and colleagues[15] found relative risks of 1.23 (95% CI 1.00–1.53) for ICU admission and 1.20 (95% CI 1.03–1.39) for death, but no association with NO_2 among people admitted to hospital with COVID-19. Using slightly different methods, a cohort study in Spain and a cohort study in the Mexico City metropolitan area also found a positive association between $PM_{2.5}$ and COVID-19 severity.[17,18] Our estimates are similar in direction of association but more modest, probably owing to differences in study population and our ability to adjust for many individual and contextual confounders. Given the ongoing pandemic, our findings that underscore the link between chronic exposure to air pollution and more severe COVID-19 could have important implications for public health and health systems.

Our study has several strengths. Our cohort captured major severe outcomes among all Ontario adults positive for SARS-CoV-2 infection who were not living in long-term care institutions. A recent modelling study identified little disparity in the officially reported COVID-19 death count and estimated excess mortality during the pandemic in Canada,[40] suggesting adequate surveillance. Using historical residential addresses in our assessment of exposure minimized concerns regarding exposure misclassification due to population mobility. We systematically considered confounding and selection bias, and estimates from the

sequential models supported our covariate adjustment strategy. For example, because residing in rural areas is often associated with lower $PM_{2.5}$ exposure[41] and was associated with lower odds of getting tested for SARS-CoV-2 infection in Ontario,[35] restricting the study population to people with positive tests might lead to an artificially diminished association between $PM_{2.5}$ and COVID-19 severity (Appendix 1, eFigure 1). The slight increases in ORs from Model 4 to Model 5 in most combinations of exposures and outcomes might have resulted from the adjustment for selection bias by including rurality (and several other contextual factors) in this step. Consistent results from the main model and sensitivity analyses also alleviated our concerns about differential results due to selection bias, residual confounding, duration of the exposure and outcome misclassification.

Limitations

Race and ethnicity have been shown to be associated with COVID-19 severity,[4] likely mediated through social determinants of health, but we did not adjust for either race or ethnicity in this study. One study[35] showed that the association between race and ethnicity and the probability of testing positive for SARS-Cov-2 infection diminished after adjusting for social determinants of health (e.g., being an essential worker), which we accounted for in this study. We believe it is unlikely that confounding related to race and ethnicity could entirely account for the associations observed.

Because we used average ambient air pollution levels at people's residential addresses as surrogates for individual exposure, some exposure misclassification is likely, owing to individuals' activity patterns, such as travel to work. However, studies have found minimal bias, or bias toward the null, from such exposure misclassification.[42,43] Generalization of our results, from all people with confirmed SARS-CoV-2 infection to all infected people, requires the assumption of similar associations between exposure to air pollution and severity of COVID-19 for those tested and not tested. Such an assumption is commonly made in studies evaluating vaccination effectiveness against clinical SARS-CoV-2 infections with a test-negative design.[44,45]

Finally, we focused on the period before widespread vaccination against SARS-CoV-2 or the use of effective medications in patients with COVID-19.

Conclusion

Using a cohort of all people with confirmed SARS-CoV-2 infection during 2020, we found empirical evidence that chronic exposure to air pollution may contribute to severe outcomes after SARS-CoV-2 infection, particularly exposure to O_3. However, uncertainty still remains in the mechanisms of how long-term air pollution might affect COVID-19 severity, which calls for future research.

References

1. COVID-19 coronavirus pandemic. Worldometer. Available: https://www.worldometers.info/coronavirus/ (accessed 2021 Nov. 17).
2. COVID-19 daily epidemiology update. aem. Ottawa: Government of Canada. Available: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html (accessed 2021 Nov. 17).
3. van Dorn A, Cooney RE, Sabin ML. COVID-19 exacerbating inequalities in the US. *Lancet* 2020;395:1243-4.
4. Millett GA, Jones AT, Benkeser D, et al. Assessing differential impacts of COVID-19 on black communities. *Ann Epidemiol* 2020;47:37-44.
5. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020;20:669-77.
6. Benmarhnia T. Linkages between air pollution and the health burden from COVID-19: methodological challenges and opportunities. *Am J Epidemiol* 2020; 189:1238-43.
7. Frontera A, Cianfanelli L, Vlachos K, et al. Severe air pollution links to higher mortality in COVID-19 patients: the "double-hit" hypothesis. *J Infect* 2020; 81:255-9.
8. Bourdrel T, Annesi-Maesano I, Alahmad B, et al. The impact of outdoor air pollution on COVID-19: a review of evidence from in vitro, animal, and human studies. *Eur Respir Rev* 2021;30:200242.
9. Marquès M, Domingo JL. Positive association between outdoor air pollution and the incidence and severity of COVID-19. A review of the recent scientific evidences. *Environ Res* 2022;203:111930.
10. Katoto PDMC, Brand AS, Bakan B, et al. Acute and chronic exposure to air pollution in relation with incidence, prevalence, severity and mortality of COVID-19: a rapid systematic review. *Environ Health* 2021;20:41.
11. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;389:1907-18.
12. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271-80.e8.
13. Paital B, Agrawal PK. Air pollution by NO_2 and $PM_{2.5}$ explains COVID-19 infection severity by overexpression of angiotensin-converting enzyme 2 in respiratory cells: a review. *Environ Chem Lett* 2021;19:25-42.
14. 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.
15. Bozack A, Pierre S, DeFelice N, et al. Long-term air pollution exposure and COVID-19 mortality: a patient-level analysis from New York City. *Am J Respir Crit Care Med* 2022;205:651-62.
16. Bowe B, Xie Y, Gibson AK, et al. Ambient fine particulate matter air pollution and the risk of hospitalization among COVID-19 positive individuals: cohort study. *Environ Int* 2021;154:106564.
17. Kogevinas M, Castaño-Vinyals G, Karachaliou M, et al. Ambient air pollution in relation to SARS-CoV-2 infection, antibody response, and COVID-19 disease: a cohort study in Catalonia, Spain (COVICAT Study). *Environ Health Perspect* 2021;129:117003.
18. López-Feldman A, Heres D, Marquez-Padilla F. Air pollution exposure and COVID-19: a look at mortality in Mexico City using individual-level data. *Sci Total Environ* 2021;756:143929.
19. Stieb DM, Evans GJ, To TM, et al. An ecological analysis of long-term exposure to $PM_{2.5}$ and incidence of COVID-19 in Canadian health regions. *Environ Res* 2020; 191:110052.
20. US EPA National Center for Environmental Assessment RTPN. Integrated science assessment (ISA) for oxides of nitrogen — health criteria (final report, Jan. 2016). Available: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310879 (accessed 2022 May 3).
21. US EPA National Center for Environmental Assessment RTPN, Luben T. Integrated science assessment (ISA) for ozone and related photochemical oxidants (final report, Apr. 2020). Available: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=348522 (accessed 2022 May 3).
22. US EPA National Center for Environmental Assessment RTPN, Sacks J. Integrated science assessment (ISA) for particulate matter (final report, Dec. 2019). Available: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534 (accessed 2022 May 3).
23. Management of cases and contacts of COVID-19 in Ontario. Version 14.1. Toronto: Ontario Ministry of Health; 2022. Available: https://www.health.gov.on.ca/en/pro/programs/publichealth/coronavirus/docs/contact_mngmt/management_cases_contacts.pdf (accessed 2022 Mar. 7).
24. Ontario Laboratories Information System (OLIS) Info. Ontario Health. Available: https://www.ehealthontario.ca/wps/portal/eHealthPortal/Applications/OlisInfo/!ut/p/z1/hc9NC4JAEAbg39LBqzOpydJtsZDsY4U0bS-hYaugrqjl30-RDkbS3GZ4XmYGOITAy-iViajNZBnlfX_l5g1dy1juiXZkvrVB6hwMi5yZjgQhGMFMUQT-L8-nxGbudiBsd_FPGuLqGzBPNweAnm3Sfof5AfM3OMBFLuPxH1rGOhHA6-SR1EmtPut-nLZt1awVVLDrOlVIKfJEvctCwV-RVDYthFMJVRFi5hYBaejiDVhspVc!/dz/d5/L2dBISEvZ0FBIS9nQSEh/ (accessed 2022 Mar. 7).

25. Chen H, Kwong JC, Copes R, et al. Cohort profile: the ONtario Population Health and Environment Cohort (ONPHEC). *Int J Epidemiol* 2017;46:405-405j.
26. van Donkelaar A, Martin RV, Li C, et al. 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* 2019;53:2595-611.
27. Hystad P, Setton E, Cervantes A, et al. Creating national air pollution models for population exposure assessment in Canada. *Environ Health Perspect* 2011;119:1123-9.
28. Robichaud A, Ménard R. Multi-year objective analyses of warm season ground-level ozone and $PM_{2.5}$ over North America using real-time observations and Canadian operational air quality models. *Atmos Chem Phys* 2014;14:1769-800.
29. Wu X, Nethery RC, Sabath MB, et al. Air pollution and COVID-19 mortality in the United States: strengths and limitations of an ecological regression analysis. *Sci Adv* 2020;6:eabd4049.
30. VanderWeele TJ, Shpitser I. A new criterion for confounder selection. *Biometrics* 2011;67:1406-13.
31. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;15:615-25.
32. Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun* 2020;11:5749.
33. Crouse DL, Peters PA, van Donkelaar A, et al. 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* 2012;120:708-14.
34. Christidis T, Erickson AC, Pappin AJ, et al. Low concentrations of fine particle air pollution and mortality in the Canadian Community Health Survey cohort. *Environ Health* 2019;18:84.
35. Sundaram ME, Calzavara A, Mishra S, et al. Individual and social determinants of SARS-CoV-2 testing and positivity in Ontario, Canada: a population-wide study. *CMAJ* 2021;193:E723-34.
36. Ontario Marginalization Index (ON-Marg). Toronto: Public Health Ontario. Available: https://www.publichealthontario.ca/en/Data-and-Analysis/Health-Equity/Ontario-Marginalization-Index (accessed 2022 Mar. 4).
37. Lee MH-Y, Xu G, Cheng F, et al. Testing surge capacity: a Canadian COVID-19 experience, Ontario's surge capacity for the first wave. *Health Policy* 2021;125:1291-6.
38. Liang D, Shi L, Zhao J, et al. Urban air pollution may enhance COVID-19 case-fatality and mortality rates in the United States. *Innovation (N Y)* 2020;1:100047.
39. Travaglio M, Yu Y, Popovic R, et al. Links between air pollution and COVID-19 in England. *Environ Pollut* 2021;268:115859.
40. Karlinsky A, Kobak D. Tracking excess mortality across countries during the COVID-19 pandemic with the World Mortality Dataset. *eLife* 2021;10:e69336.
41. Pinault L, van Donkelaar A, Martin RV. Exposure to fine particulate matter air pollution in Canada. *Health Rep* 2017;28:9-16.
42. Richmond-Bryant J, Long TC. Influence of exposure measurement errors on results from epidemiologic studies of different designs. *J Expo Sci Environ Epidemiol* 2020;30:420-9.
43. Samoli E, Butland BK, Rodopoulou S, et al. The impact of measurement error in modeled ambient particles exposures on health effect estimates in multilevel analysis: a simulation study. *Environ Epidemiol* 2020;4:e094.
44. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013;31:2165-8.
45. Vandenbroucke JP, Brickley EB, Vandenbroucke-Grauls CMJE, et al. A test-negative design with additional population controls can be used to rapidly study causes of the SARS-CoV-2 epidemic. *Epidemiology* 2020;31:836-43.

Competing interests: Jeff Kwong is supported by a Clinician Scientist Award from the Department of Family and Community Medicine, University of Toronto. Chen Chen reports receiving salary support by the funding of this project, from Health Canada. Megan Kirby-Mcgregor reports receiving doctoral student funding from Health Canada, paid through McGill University. Jay Kaufman reports receiving payments from Health Canada (paid to institution) for student salaries and other research expenses associated with this work. Hong Chen reports receiving support for the present manuscript from Health Canada. No other competing interests were declared.

This article has been peer reviewed.

Affiliations: Scripps Institution of Oceanography (C. Chen, Benmarhnia), University of California San Diego, La Jolla, Calif.; Public Health Ontario (Wang, Kwong, Kim, H. Chen); ICES Central (Kwong, H. Chen); Dalla Lana School of Public Health (Kwong, Kim, H. Chen), and Department of Family and Community Medicine (Kwong), University of Toronto, Toronto, Ont.; Department of Energy, Environmental, and Chemical Engineering (van Donkelaar, Martin), Washington University in St. Louis, St. Louis, Mo.; College of Public Health and Human Studies (Hystad), Oregon State University, Corvallis, Ore.; Ontario Ministry of the Environment (Su), Conservation and Parks, Toronto, Ont.; Environmental Health Science and Research Bureau (Lavigne, H. Chen), Health Canada, Ottawa, Ont.; Department of Epidemiology and Biostatistics and Occupational Health (Kirby-McGregor, Kaufman), McGill University, Montréal, Que.

Contributors: Chen Chen, Megan Kirby-McGregor, Jay Kaufman, Tarik Benmarhnia and Hong Chen contributed to the conception of the work. Chen Chen, John Wong, Megan Kirby-McGregor, Jay Kaufman, Tarik Benmarhnia, Jeff Kwong, JinHee Kim, Aaron van Donkelaar, Randall Martin, Perry Hystad, Yushan Su, Eric Lavigne and Hong Chen contributed to the design of the work. John Wong, Jeff Kwong, JinHee Kim, Aaron van Donkelaar, Randall Martin, Perry Hystad, Yushan Su, Eric Lavigne and Hong Chen contributed to the acquisition of data. Chen Chen, John Wong, Jay Kaufman, Tarik Benmarhnia and Hong Chen contributed to the analysis of data. All of the authors contributed to the interpretation of the data. Chen Chen, Jay Kaufman, Tarik Benmarhnia and Hong Chen drafted the manuscript. All of the authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Content licence: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: https://creativecommons.org/licenses/by-nc-nd/4.0/

Funding: This study was funded by Health Canada (No. 810630).

Data sharing: The data set from this study is held securely in coded form at ICES. While legal data-sharing agreements between ICES and data providers (e.g., health care organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Disclaimer: This study was funded by the Addressing Air Pollution Horizontal Initiative of the Government of Canada; it was also supported by Public Health Ontario (PHO) and ICES, which are funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). Parts of this material are based on data and information compiled and provided by the Ontario MOH and the Canadian Institute for Health Information (CIHI) and on information on cancers provided by Cancer Care Ontario (CCO). However, the analyses, conclusions, opinions, and statements expressed herein are not necessarily those of CIHI, PHO, ICES, the Ontario MOH, the Ontario MLTC or CCO. No endorsement by ICES, the Ontario MOH or the Ontario MLTC is intended or should be inferred.

Accepted: Apr. 27, 2022

Correspondence to: Chen Chen, chc048@ucsd.edu;
Hong Chen, hong.chen@hc-sc.gc.ca