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

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## 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<sub>2.5</sub>), nitrogen dioxide (NO<sub>2</sub>) and

ground-level ozone (O<sub>3</sub>), 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<sub>2.5</sub> (1.70 µg/m<sup>3</sup>), 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<sub>2</sub>. 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<sub>3</sub> 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<sub>3</sub>.

By November 2021, COVID-19 had caused more than 5 million deaths globally<sup>1</sup> and more than 29 400 in Canada.<sup>2</sup> 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.<sup>3–5</sup> More recently, ambient air pollution has been implicated as a potential driver of COVID-19 severity.<sup>6–10</sup>

Long-term exposure to ambient air pollution, a major contributor to global disease burden,<sup>11</sup> 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.<sup>8</sup> Air pollution can also induce chronic inflammation and overexpression of the alveolar angiotensin-converting enzyme 2 (ACE) receptor,<sup>7</sup> the key receptor that facilitates SARS-CoV-2 entry into cells.<sup>12,13</sup> 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.<sup>10</sup> 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<sub>2.5</sub> and PM<sub>10</sub>), ground-level ozone (O<sub>3</sub>) and nitrogen dioxide (NO<sub>2</sub>), and metrics of COVID-19 severity

(e.g., mortality and case fatality rate).<sup>8–10</sup> 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.<sup>6,14</sup> Ecological designs do not allow for disentangling the relative impacts of air pollution on individual susceptibility to infection and disease severity.<sup>14</sup> 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.<sup>6,14</sup> Studies that have used individual data were conducted in specific subpopulations<sup>15,16</sup> or populations with few severe cases,<sup>17</sup> or had limited data on individual exposure to air pollutants.<sup>18</sup> In Canada, 1 ecological study found a positive association between long-term exposure to PM<sub>2.5</sub> and COVID-19 incidence,<sup>19</sup> 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<sub>2.5</sub>, NO<sub>2</sub> and O<sub>3</sub>) 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<sub>2.5</sub>, NO<sub>2</sub> and O<sub>3</sub> 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<sub>2</sub> is primarily emitted during combustion of fuel, O<sub>3</sub> is primarily formed in air by chemical reactions of nitrogen oxides and volatile organic compounds, and PM<sub>2.5</sub> 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.<sup>20,21,22</sup>

## 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.<sup>23,24</sup> 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](http://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.<sup>25</sup> We used annual exposure surfaces of PM<sub>2.5</sub>, NO<sub>2</sub> and O<sub>3</sub> developed previously, which showed good performance in evaluations: the PM<sub>2.5</sub> surface exhibited  $R^2 = 0.73$  in long-term cross-validation with measurements;<sup>26</sup> the NO<sub>2</sub> model accounted for 73% of the variability in annual measurements;<sup>27</sup> and the O<sub>3</sub> model's proportion of correct predicted values ranged from 65% to 93%, depending on the time of day<sup>28</sup> (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<sub>2.5</sub>, O<sub>3</sub> and NO<sub>2</sub>) 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.<sup>14,16,29</sup> We applied the “disjunctive cause criterion,” which includes any pre-exposure covariate that is a cause of the exposure or the outcome, or both.<sup>30</sup> 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.<sup>31</sup> 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).<sup>32</sup> Using literature on air pollution and health in Canada,<sup>33,34</sup> evidence about the drivers of COVID-19 severity<sup>3–5,16</sup> and recently identified contextual factors associated with testing positive for SARS-CoV-2 infection in Ontario,<sup>35</sup> 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.<sup>36</sup> 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),<sup>37</sup> 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.

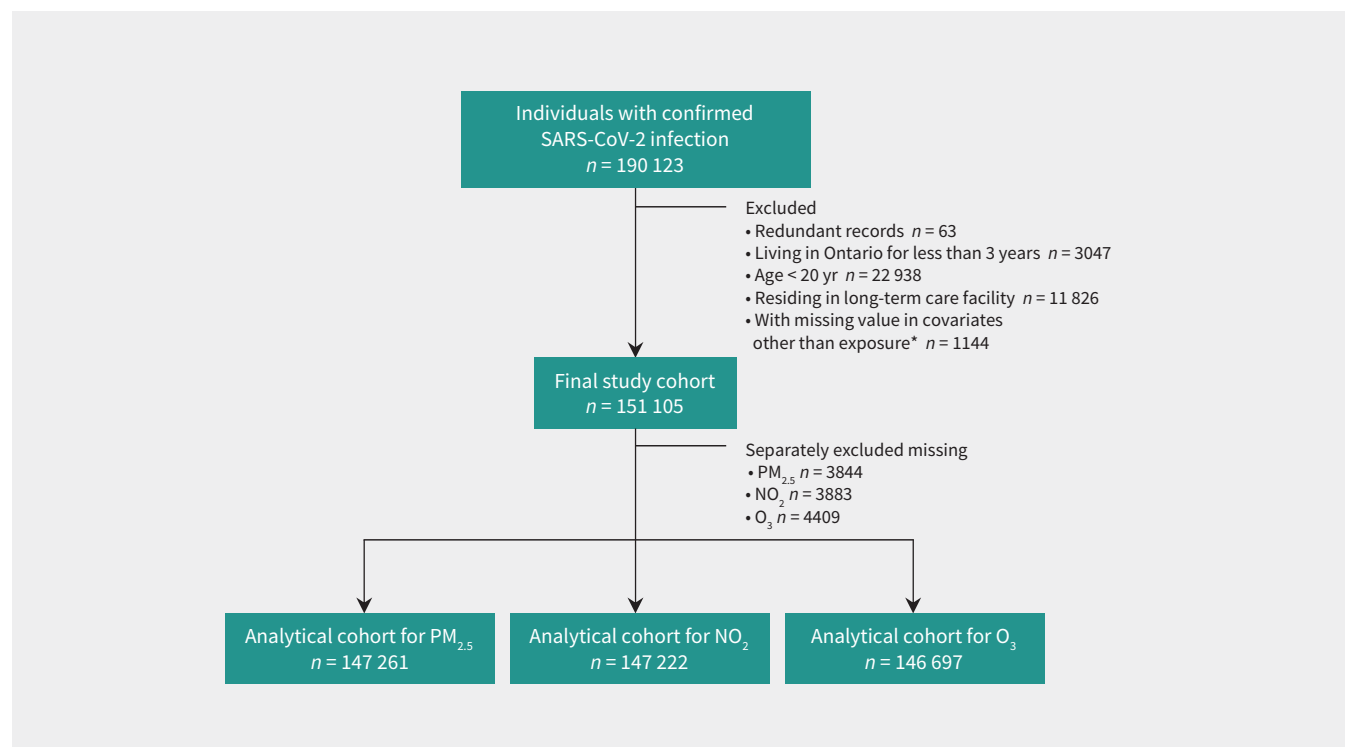
## Results

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  $\mu\text{g}/\text{m}^3$  (6.43–8.13), 7.75 ppb (6.15–8.65) and 44.80 ppb (42.41–47.38) for  $\text{PM}_{2.5}$ ,  $\text{NO}_2$  and  $\text{O}_3$ , respectively. Cohort characteristics are summarized by outcome in Table 1 and by exposure in Appendix 1, eTable 2.

Higher exposure to  $\text{PM}_{2.5}$  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  $\mu\text{g}/\text{m}^3$  for hospital admission and ICU admission, respectively (Appendix 1, eTable 4). Although death was positively associated with  $\text{PM}_{2.5}$  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  $\text{NO}_2$ , we found similar patterns in results of sequential models (1–4) as for  $\text{PM}_{2.5}$ . In the fully adjusted model, we obtained ORs of 1.09 (95% CI 0.97–1.21) per IQR increase of 2.50 ppb  $\text{NO}_2$  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  $\text{O}_3$ , 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<br>n = 151 105 | No. (%)* of people admitted to hospital<br>n = 8630 | No. (%)* of people admitted to ICU<br>n = 1912 | No. (%)* of people who died<br>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<br>n = 151 105 | No. (%)* of people admitted to hospital<br>n = 8630 | No. (%)* of people admitted to ICU<br>n = 1912 | No. (%)* of people who died<br>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 <sup>2</sup> , 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.

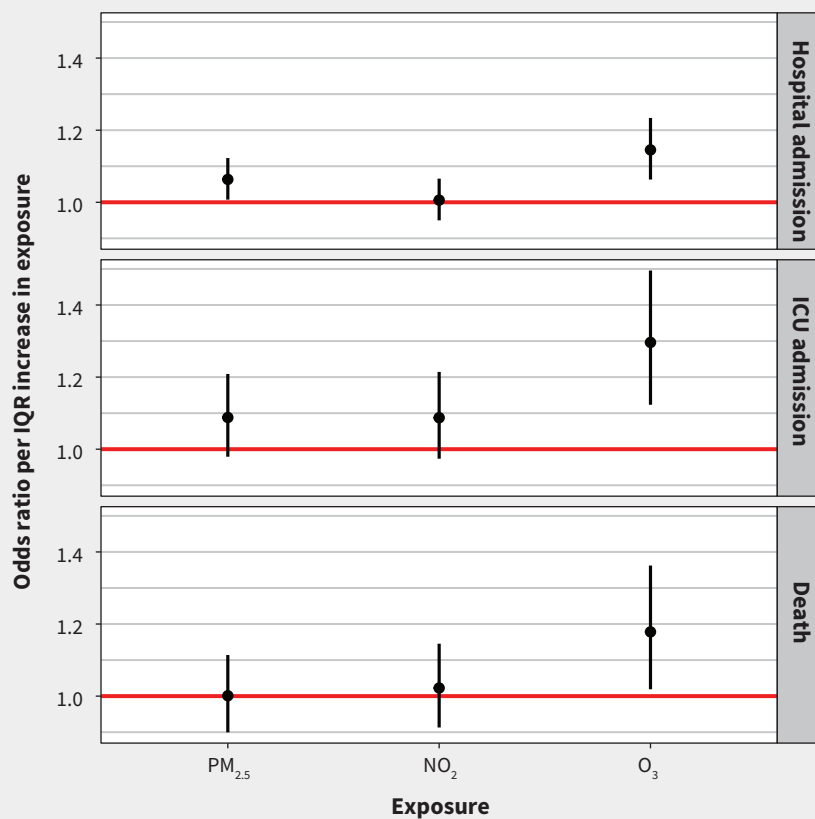
§We define distance to nearest health services as the distances of a dissemination block to any dissemination block with a health care facility. The original distance was normalized.

¶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<sub>3</sub> 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<sub>3</sub> but attenuated for NO<sub>2</sub> and PM<sub>2.5</sub> 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<sub>2.5</sub>, NO<sub>2</sub> and O<sub>3</sub>) 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<sub>2.5</sub> and O<sub>3</sub> was associated with elevated risk of COVID-19–related hospital admission, and exposure to O<sub>3</sub> 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<sub>3</sub>.

Previous ecological studies found positive associations between long-term exposure to PM<sub>2.5</sub>, NO<sub>2</sub> and O<sub>3</sub>, and COVID-19 mortality and case fatality rate.<sup>29,38,39</sup> 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<sup>3</sup> increase in PM<sub>2.5</sub> concentration

for hospital admission among American veterans who received a diagnosis of COVID-19,<sup>16</sup> while Bozack and colleagues<sup>15</sup> 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<sub>2</sub> 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<sub>2.5</sub> and COVID-19 severity.<sup>17,18</sup> 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,<sup>40</sup> 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<sub>2.5</sub> exposure<sup>41</sup> and was associated with lower odds of getting tested for SARS-CoV-2 infection in Ontario,<sup>35</sup> restricting the study population to people with positive tests might lead to an artificially diminished association between PM<sub>2.5</sub> 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,<sup>4</sup> likely mediated through social determinants of health, but we did not adjust for either race or ethnicity in this study. One study<sup>35</sup> 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.<sup>42,43</sup> 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.<sup>44,45</sup>

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<sub>3</sub>. However, uncertainty still remains in the mechanisms of how long-term air pollution might affect COVID-19 severity, which calls for future research.

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