Differential patterns by area-level social determinants of health in COVID-19 related mortality and non-COVID-19 mortality: a population-based study of 11.8 million people in Ontario, Canada

Authors: Linwei Wang, MSc[1], Andrew Calzavara, MSc[2], Stefan Baral, MD[3], Janet Smylie, MD[1,4,5], Adrienne K. Chan, MD[5,6,7,8], Beate Sander, PhD[2,7,9,10], Peter C. Austin, PhD[2,7,8], Jeffrey C. Kwong, MD [2,5,10,11,12], Sharmistha Mishra, PhD[1,5,6,7,13]

Affiliations: [1]MAP-Centre for Urban Health Solutions, St. Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada; [2]ICES, Toronto, ON, Canada; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [4]Well Living House, Toronto, ON, Canada; [5]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; [6]Department of Medicine, University of Toronto, Toronto, ON, Canada; [7]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada; [8]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [9]Toronto Health Economics and Technology Assessment (THETA) Collaborative, University Health Network, Toronto, Canada; [10]Public Health Ontario, Toronto, ON, Canada; [11]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada; [12]University Health Network, Toronto, ON, Canada; [13]Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

Corresponding Author:
Sharmistha Mishra, MD, MSc, PhD
MAP-Centre for Urban Health Solutions
St. Michael's Hospital, Unity Health Toronto
University of Toronto
209 Victoria St, Toronto, ON, Canada, M5B 1T8
E: sharmistha.mishra@utoronto.ca

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ABSTRACT

Background: Social determinants of health (SDOH) have been associated with COVID-19 outcomes. We examined differential patterns in COVID-19-related mortality by SDOH accounting for confounders and compared these patterns to those for non-COVID-19 mortality.

Methods: Residents of Ontario, Canada aged ≥20 years were followed from March-01-2020 to March-02-2021. COVID-19-related death was defined as death within [-7,30] days of a positive COVID-19 test. Area-level SDOH from 2016 Census included: median household income; proportion with diploma or higher educational-attainment; proportion essential workers, racially-minoritised groups, recent immigrants, apartment buildings, and high-density housing; and average household size. We examined associations between SDOH and COVID-19-related mortality using cause-specific hazard models, treating non-COVID-19 mortality as competing risks, and vice-versa.

Results: Of 11,810,255 individuals, we observed 3,880(0.03%) COVID-19-related deaths and 88,107(0.75%) non-COVID-19 deaths. After accounting for individual-level demographics, baseline health, and other area-level SDOH, the following area-level SDOH were associated with increased hazards of COVID-19-related death (hazard ratios[95% confidence intervals]: lower income (1.30[1.04-1.62]), lower educational-attainment (1.27[1.07-1.52]), higher proportions essential workers (1.28[1.05-1.57]), racially-minoritised groups (1.42[1.08-1.87]), apartment buildings (1.25[1.07-1.46]), and large vs. medium household size (1.30[1.12-1.50]). In comparison, areas with higher proportion racially-minoritised groups were associated with a lower hazard of non-COVID-19 mortality (0.88[0.84-0.92]).

Conclusions: Area-level SDOH are associated with COVID-19-related mortality after accounting for demographic and clinical factors. COVID-19 has reversed patterns of lower non-COVID-19 mortality among racially-minoritised groups vs. their counterparts. Pandemic

responses should include strategies (e.g., 'hotspot' and risk-group tailored vaccination) to address disproportionate risks and inequitable reach of, and access to, preventive interventions associated with SDOH.

Key words: social determinants of health, COVID-19, mortality, case fatality, inequality; race/ethnicity; socioeconomic status

INTRODUCTION

Increasing evidence has confirmed the central role of social determinants of health (SDOH) in shaping variations in COVID-19 disease burden and severity(1-6). Across high-income countries, rates of COVID-19 diagnoses and deaths have been consistently correlated with socioeconomic status (SES)(5, 7), and disproportionately affecting racially-minoritised groups(3, 8-10).

In the context of infectious disease, social and structural inequalities may shape differential health outcomes through differences in susceptibility, contact patterns and networks (11, 12), and reach/uptake of prevention interventions (e.g., access to testing(12, 13), effective isolation and quarantine(14), ability to reduce non-household contacts(15), access to vaccines(16)); and quality of treatment(17, 18).

To date, most studies have focused on SDOH such as SES as a composite index(5, 6, 13) and race/ethnicity as proxies for structural racism (biological differences(19), if any, are not the sole explanation for observed disparities by race/ethnicity)(3, 8, 10). Few studies have examined other SDOH such as educational-attainment, occupation and housing conditions, and even fewer have examined several SDOH in conjunction(1, 2). Moreover, studies on the relationship between SDOH and COVID-19 death were often conducted among diagnosed cases, or

hospitalized populations(7). Although outcomes such as case fatality among diagnosed cases and mortality while hospitalized provided important information regarding disease severity by SDOH, these analyses are prone to collider biases(20). For example, SDOH and severe COVID-19 outcomes both affect likelihoods of being diagnosed/hospitalized; restricting analyses amongst samples of diagnosed/hospitalized cases could distort the relationship between SDOH and COVID-19 outcomes(3, 5, 7).

In Canada, provisional Vital Statistics Deaths data have demonstrated higher age-standardized COVID-19-related mortality among urban residents (vs. rural), lower income areas, higher ethno-cultural concentration areas, and residents of apartment buildings (vs. detached homes)(21). However, existing studies were not able to account for potential confounders such as comorbidities. Moreover, to date, no studies have estimated COVID-19-related mortality while at the same time accounting for mortality unrelated to COVID-19, which is a competing risk for COVID-19-related mortality(22). Such an inquiry provides opportunities to understand whether the same patterns of inequities drive both COVID-19 and non-COVID-19-related mortality.

Using population-based data among 11.8 million adults in Ontario, Canada, we examined differential patterns in COVID-19-related mortality across a set of area-level SDOH including SES (median household income, proportion with diploma or higher educational-attainment, proportion essential workers), ethnic diversity (proportion racially-minoritised groups, proportion recent immigrations) and housing conditions (proportion apartment buildings, proportion high-density housing, average household size). We assessed whether patterns in COVID-19-related mortality by SDOH can be explained by demographics, baseline health, and other area-level SDOH. We also compared patterns by SDOH in COVID-19-related mortality versus those in non-COVID-19 mortality, and in COVID-19 case fatality.

METHODS

Study design and subjects

We conducted a population-based retrospective cohort study of community-dwelling adults in Ontario, Canada, a setting with universal health care (23). Individuals aged ≥20 years residing in Ontario as of March 1, 2020 and having a valid health card were identified using Ontario's Registered Persons Database (RPDB), and followed through March 2, 2021. We excluded residents in long-term care homes because they are not included in Canadian census data from which SDOH variables were determined(24, 25). Data use was authorized under Section 45 of Ontario's Personal Health Information Protection Act, which does not require Ethics review.

Outcomes

Our primary outcome was COVID-19-related death, defined as death within 30 days following, or 7 days prior to a positive COVID-19 test. Test result and date were determined based on records in the Ontario Laboratories Information System and the Public Health Case and Contact Management Solution (CCM). Date of death was determined using CCM and RPDB. We estimated that use of both CCM and RPDB capture 99.3% of COVID-19-related deaths (**Appendix-Table-1**). The secondary outcome was non-COVID-19 death, defined as death without any history of a positive COVID-19 test. COVID-19-related mortality, and non-COVID-19 mortality were estimated using the full cohort as the denominator. COVID-19 case fatality was estimated using the subset of the cohort that was diagnosed with COVID-19 as the denominator.

We restricted our analyses to COVID-19-related deaths observed up to March 2, 2021 and cases diagnosed prior to January 31, 2021. Therefore, our analyses capture the first and second waves of regional pandemic representing the original strain of the virus (>95%) or the alpha variant (26, 27).

Covariates

Based on available data and existing literature(4, 7, 8, 10, 12, 28), we developed a conceptual framework to select SDOH variables, and potential confounders for the relationship between SDOH and outcomes, as hypothesized along the risk pathway of COVID-19-related mortality, including risk of infection, risk of testing if infected, and risk of death if diagnosed; with rationales of variable selection detailed in **Figure-1**.

Our primary covariates included area-level SDOH, derived from the 2016 Census at dissemination areas (DA) level, the smallest geographic unit (representing 400-700 residents) for which census data are reported (24). Area-level SDOH included factors reflecting SES (median household income, proportion with diploma or higher educational-attainment, proportion essential workers), ethnic diversity (proportion racially-minoritised groups, proportion recent immigrants), and housing conditions (proportion apartment buildings, proportion high-density housing, average household size). Proportion essential workers was defined as the proportion of working people in the DA who self-identify as working in sales, trades, manufacturing, and agriculture. Proportion racially-minoritised groups was defined as the proportion of people who self-identify as non-White and non-Indigenous. Proportion apartment buildings was defined as the proportion of buildings which are apartments. For each SDOH variable, we ranked DAs at the city (for income) or provincial level (for other SDOH) and then categorized them into quintiles. For example, a DA being in income quintile 1 means it is among

the highest 20% of DAs in its city by median household income. Detailed definitions of these variables are shown in **Table-1 footnotes.**

All covariates other than SDOH were measured at the individual-level, including age, sex (male vs. female), other demographics (living in rural(29) vs. urban; public health region), and baseline health (a set of comorbidity variables (**Table-1**); past 3-year hospital admission; past year outpatient physician visits).

All data sets were linked using unique encoded identifiers(30) and analyzed at ICES.

Statistical analysis

We examined and compared the demographics, baseline health, and SDOH of the full cohort, individuals who died related to COVID-19, and individuals who died without COVID-19 using descriptive statistics.

To examine the relationship between SDOH and COVID-19-related mortality, we employed cause-specific hazard models(22, 31), where deaths without a positive COVID-19 test were treated as competing risk events (**Appendix-Figure-1**). We proposed *a priori* and fitted unadjusted, and a set of adjusted models with serial adjustment to assess the impact of different confounders. The models were fitted using the PHREG procedure of SAS(32). Proportional hazard assumptions were assessed using the scaled Schoenfeld residuals tests(33)(**Appendix-Table-2**).

To compare patterns by SDOH in non-COVID-19 mortality to those in COVID-19-related mortality, we repeated analyses using cause-specific hazard models to examine relationship between SDOH and non-COVID-19 mortality, treating COVID-19 diagnosis as a competing risk.

To compare patterns by SDOH in COVID-19-related mortality to those in COVID-19 case fatality, we employed multivariable logistic regression models to examine the associations between SDOH and COVID-19-related death among those who tested positive for COVID-19.

To quantify the absolute differences by area-level SDOH in COVID-19-related mortality, we employed Fine & Gray subdistribution hazard models(22, 34). Based on the fitted models adjusted for individual-level demographics and baseline health, we estimated the adjusted marginal cumulative incidence functions(35), and calculated the difference in the one-year cumulative probability of COVID-19-related death between the most (SDOH level with the worst outcome; e.g., lowest income quintile) and the least (SDOH level with the best outcome; e.g., highest income quintile) at risk group for each SDOH variable.

All analyses were conducted using SAS 9.4(32). R 4.1.2 was used to generate figures(36). The confidence intervals (CIs) were derived from a robust sandwich covariance matrix to account for clustering by DA(37).

RESULTS

Of 11,810,255 community-dwelling adults (median age 48 years) included, 206,671(1.75%) tested positive for COVID-19, 3880(0.03%) died related to COVID-19, and 88,107(0.75%) died

without a COVID-19 diagnosis. Individuals with missing data (N=111,955(0.9%)) on area-level SDOH were excluded from the multivariable regression analyses (**Appendix-Figure-2**).

Deaths related to COVID-19 were disproportionately concentrated among older adults, males and individuals living in urban areas(**Table-1**). COVID-19-related deaths were also disproportionately concentrated among individuals living with a comorbidity and those with more prior healthcare use (**Table-1**). Compared to the full cohort, COVID-19-related deaths were overrepresented in areas with less social advantage (e.g. 28.9% vs.19.5% lived in the lowest-income areas); and in areas with higher proportion racially-minoritised groups (38.7% vs. 27.3%) and recent immigrants (37.7% vs. 27.4%) (**Table-1**).

Area-level SDOH and COVID-19-related mortality

In the unadjusted models, areas with lower SES, higher ethnic diversity, higher proportion of apartment buildings and high-density housing, and the lowest or highest household size (vs. medium) were associated with increased hazard of COVID-19-related death (**Figure-2A, Appendix-Table-3**). We observed a dose-response relationship between all area-level SDOH variables and COVID-19-related mortality, except for household size (medium household size was associated with the lowest COVID-19-related mortality and was treated as reference group) (**Figure-2**).

Adjustment for individual-level demographics either attenuated or amplified the associations between COVID-19-related mortality and area-level SES (**Figure-2A-2C**). Further adjustment for baseline health slightly reduced the associations between COVID-19-related mortality and SES (**Figure-2C-2D**). After further adjustment for other area-level SDOH, SES remained an independent determinant of COVID-19-related mortality, although the magnitude of association

was greatly reduced (**Figure-2D-2E**). Fully adjusted hazard ratios (aHRs) and 95% CIs were 1.30[1.04,1.62] for lowest vs. highest income, 1.27[1.07,1.52] for lowest vs. highest proportion with diploma or higher educational-attainment, and 1.28[1.05,1.57] for highest vs. lowest proportion essential workers (**Figure-2E and Appendix-Table-3**).

Adjustment for age and sex increased the magnitude of associations between area-level ethnic diversity and COVID-19-related mortality (**Figure-2A-2B**). Additional adjustment for other individual-level demographics largely reduced the magnitude of associations (**Figure-2B-2C**). Further adjustment for baseline health had a minimal influence on the associations (**Figure-2C-2D**). Additional adjustment of other area-level SDOH reduced the magnitude of associations between COVID-19-related mortality and proportion racially-minoritised groups, and nullified the association between COVID-19-related mortality and proportion recent immigrants (**Figure-2D-2E**). Fully adjusted aHR and 95% CI were 1.42[1.08,1.87] for highest vs. lowest proportion racially-minoritised groups (**Figure-2E and Appendix-Table-3**).

After adjustment for individual-level demographics and baseline health, and other area-level SDOH, proportion apartment buildings was independently associated with increased hazard of COVID-19-related death (1.25[1.07,1.46]); while proportion high-density housing was not (**Figure-2E**; **Appendix-Table-3**). The non-monotonic relationship between COVID-19-related mortality and area-level household size persisted after full adjustment. Fully adjusted aHR and 95% CI were 1.30[1.12,1.50] for highest vs. medium area-level household size (**Figure-2E and Appendix-Table-3**).

Area-level SDOH and non-COVID-19 mortality, and COVID-19 case fatality

In contrast to the pattern with COVID-19-related mortality, areas with higher proportion racially-minoritised groups (highest vs. lowest: 0.88[0.84,0.92]), and large household size (highest vs medium: 0.85[0.83,0.88]) were independently associated with decreased hazard of non-COVID-19 death (**Figure-3A-3B and Appendix-Table-4**).

Only lower area-level income was independently associated with increased COVID-19 case fatality (**Figure-3C and Appendix-Table-4**).

Adjusted cumulative probability of COVID-19-related death

After accounting for individual-level demographics and baseline health, the estimated absolute difference in the cumulative probability of COVID-19-related death over a one-year period ranged from 0.006% to 0.020%, comparing the most and least at risk SDOH group (**Figure-4**).

DISCUSSION

In a population-based cohort of 11.8 million adults in Ontario, Canada, we found that areas characterized by lower SES, greater ethnic diversity, more apartment buildings, and large vs. medium household size were associated with increased hazards of COVID-19-related mortality, after accounting for individual-level demographics, baseline health, and other area-level SDOH. In contrast, areas with higher proportion racially-minoritised groups and larger household size were associated with reduced hazard of non-COVID-19 mortality. With the exception of income, the area-level SDOH examined in this study were not independently associated with COVID-19 case fatality.

Our findings mirror studies in other countries, including the UK(4), Switzerland(5), Chile(13), and the US(6), which have shown that areas with lower SES, measured by a composite index, were associated with increased risk and mortality of COVID-19. Our study demonstrated that specific elements of area-level SES, including income, educational attainment, and essential workers were each independently associated with elevated hazard of COVID-19-related mortality. For example, individuals working in front-facing essential services that were not amenable to remote work had limited ability to shelter-in-place during periods of broad-scale restrictions on mobility, and were less likely to receive benefits such as paid sick leave(38, 39), leading to heightened exposure risk and barriers to effective quarantine or isolation(12, 14). The relationship between area-level income and case-fatality might reflect delayed diagnosis or access to and quality of clinical care for persons living in lower income neighbourhoods(17, 40, 41). Emerging evidence suggests that in-hospital mortality with COVID-19 was amplified during periods of higher patient load; such inpatient surges were most likely to occur in hospitals serving lower income areas experiencing the highest rates of cases(17, 40-42).

Our finding that areas with a higher proportion racially-minoritised groups experienced increased hazard of COVID-19-related mortality but not higher case-fatality confirmed findings in other settings(3, 10). A systematic review of 52 US studies found that African-American/Black and non-white Hispanic populations experienced a disproportionate burden of infections, hospitalization, and COVID-19-related mortality, but not higher in-hospital case-fatality, compared to similarly aged white non-Hispanic populations(10). Studies in the UK found that minority ethnic groups experienced elevated risk of COVID-19-related mortality(3), higher prevalence of COVID-19 antibodies(43), but similar infection fatality ratio(43) compared to white counterparts. Taken together, the findings suggest that inequalities in COVID-19-related mortality by racially-minoritised groups are more likely to stem from disproportionate exposure

risks leading to disproportionate risks of acquisition/ transmission, and barriers to the reach/access to, preventive interventions, as opposed to differences post-diagnosis (3, 10, 12).

In Canada, racially-minoritised groups are more likely to work in essential services and more likely to live in larger and higher-density households(44)– all of which have been identified as mechanistic risk factors for heightened exposure risk(12, 14). Prior to COVID-19 and similar to our findings regarding non-COVID-19 mortality during the COVID-19 pandemic, mortality rates in Canada were lower in racially-minoritised groups(45). Similar to findings from the UK and Sweden (3, 46), COVID-19 has reversed the dose-response pattern of lower non-COVID-19 mortality among racially-minoritised groups vs. their counterparts.

The non-monotonic relationship between area-level household size and COVID-19-related mortality might be partially explained by the positive correlation between income and household size (data not shown); and by different contact patterns (e.g., individuals living by themselves might have might have increased contacts outside household). Our findings suggest that large household size, regardless of the housing density, might be an independent risk factor for household transmission. In epidemic theory, contact rates are conceptualized as density-dependent or frequency-dependent. Transmissions outside households may be influenced by population density (density-dependent transmission)(47). Within the same household, contact rates may be better reflected by the frequency-dependent transmission (thus, household size; i.e., assumingclose interactions among all household members, regardless of the household density)(47).

Strengths of our study include limiting collider bias(20) and leveraging high-quality linked health administrative, surveillance, and health registries data to examine the influence of various confounders, including comorbidities, on the relationship between COVID-19-related mortality

and area-level SDOH. Another strength is the competing risk survival analysis approach which allowed us to correctly estimate the marginal probability of COVID-19-related death in the presence of competing events. Our estimates of marginal probability of COVID-19-related death by area-level SDOH provided important insights into the health of each subgroup, and permitted the quantification of inequalities on an absolute scale with adjustment of covariates (3, 5, 48); which are meaningful for public health decision-making including informing strategies such as geographically-focused vaccination (49-51).

Limitations include the potential for misclassification due to lack of data on the cause of death. Based on Ontario COVID-19 surveillance data, 92% of recorded all-cause deaths among individuals diagnosed with COVID-19 occurred within 30 days following or 7 days prior to a positive test (**Appendix-Figure-3**). Other settings have adopted similar definitions of COVID-19-related death to capture the immediate impact of COVID-19 on death(52). Our estimates of COVID-19-related mortality might be underestimated if missed diagnosis occurs due to lack of testing, or false negative antigen tests(53). Individuals who do not have provincial health insurance were not captured; and if they were more likely to be socially and structurally vulnerable, our estimates might have under-estimated the inequalities. We were restricted to area-level SDOH measures in the absence of individual-level measures, which might result in an underestimation of the SDOH-mortality associations(54). Almost all areas with the highest quintile proportion racially-minoritised groups were urban areas. However, stratified analysis by rural/urban revealed that inequalities in COVID-19-related mortality by racially-minoritised groups were present in both settings (**Appendix-Table-5**). We lacked data on the severity of comorbidities and COVID-19 infection, and individuals' exposures related to contact patterns and physical networks (e.g., mobility, physical distancing) and masking, information that could help further explain the relationship between SDOH and COVID-19-related mortality. We did not evaluate if the associations between SDOH and COVID-19-related mortality differed across age

groups or regions, or changed over time (e.g., between pandemic waves, or in the context of vaccination)(3, 13); which will be an important next step of research. Indeed, examination of proportional hazard assumptions suggest a time-varying relationship between proportion racially-minoritised group and hazard of COVID-19-related mortality (**Appendix-Table-2**).

Our study demonstrated that area-level social and structural inequalities are associated with COVID-19-related mortality after accounting for age, sex, and clinical factors. The majority of inequalities stem from proximal exposures and reach of, and access to, prevention interventions. COVID-19 has reversed existing patterns of mortality by race/ethnicity, with higher COVID-19-related mortality for racially-minoritised groups. Tailored strategies that specifically address and are designed around the risk pathways related to SES, racism, and housing contexts, include but are not limited to: paid sick leave and improved workplace health and safety protocols and outbreak management; and community-led and community-tailored outreach for testing, effective isolation and quarantine and vaccine programs. Moving forward, the goal of pandemic responses should include improving overall population health by addressing disproportionate acquisition and transmission risks and inequitable coverage of prevention interventions associated with SDOH.

NOTES

Contribution: LW, JCK, and SM conceptualized the study. AC conducted the data cleaning and statistical analyses. LW drafted the manuscript. AC, SB, JS, AKC, BS, PCA, JCK, and SM provided critical inputs into the results interpretation and manuscript.

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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 www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset 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.

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Table 1. Characteristics* of overall community dwelling adults in Ontario and those died related to COVID-19 and other causes.

	Number of individuals residing in Ontario as of Mar 1, 2020	Number of COVID-19-related deaths[a] between Mar 1, 2020 and Mar 2, 2021	Number of non-COVID-19 deaths[b] between Mar 1, 2020 and Mar 2, 2021
Total	11,810,255	3,880	88,107
Age (Median (interquartile range))[c]	48 (34-62)	81 (72-88)	77 (65-86)
Age category[c]			
20-34	3,143,764 (26.6%)	23 (0.6%)	2,289 (2.6%)
35-49	3,009,493 (25.5%)	84 (2.2%)	4,149 (4.7%)
50-64	3,099,010 (26.2%)	399 (10.3%)	14,334 (16.3%)
65-74	1,487,522 (12.6%)	710 (18.3%)	17,897 (20.3%)
75-84	769,255 (6.5%)	1,140 (29.4%)	22,900 (26.0%)
85+	301,211 (2.6%)	1,524 (39.3%)	26,538 (30.1%)
Male	5,777,603 (48.9%)	2,249 (58.0%)	48,501 (55.0%)
Residing in a rural area[d]	1,192,569 (10.1%)	138 (3.6%)	11,614 (13.2%)
Comorbidities[e]			
Asthma	1,750,679 (14.8%)	752 (19.4%)	14,671 (16.7%)
Chronic obstructive pulmonary disease	290,131 (2.5%)	643 (16.6%)	17,064 (19.4%)
Hypertension	3,085,359 (26.1%)	3,205 (82.6%)	63,356 (71.9%)
Diabetes	1,471,040 (12.5%)	1,847 (47.6%)	32,328 (36.7%)
Congestive heart failure	264,194 (2.2%)	988 (25.5%)	22,696 (25.8%)
Dementia or frailty score >15[f]	164,518 (1.4%)	1,215 (31.3%)	18,742 (21.3%)
Cancer[g]	242,667 (2.1%)	235 (6.1%)	15,663 (17.8%)
Chronic kidney disease[h]			
With no recent dialysis	277,564 (2.4%)	937 (24.1%)	16,286 (18.5%)
With recent (last 3-month) dialysis	11,131 (0.1%)	95 (2.4%)	1,723 (2.0%)
Immunocompromised[i]	89,318 (0.8%)	130 (3.4%)	3,997 (4.5%)
Advanced Liver Disease[j]	86,612 (0.7%)	103 (2.7%)	4,337 (4.9%)
Cardiac ischemic disease[k]	359,120 (3.0%)	707 (18.2%)	15,166 (17.2%)
Ischemic stroke or transient ischemic attack[l]	112,634 (1.0%)	370 (9.5%)	6,994 (7.9%)
Hospital admission, past 3 years			
0	10,278,277 (87.0%)	1,934 (49.8%)	40,188 (45.6%)
Once	1,112,902 (9.4%)	856 (22.1%)	20,623 (23.4%)
Twice	265,192 (2.2%)	503 (13.0%)	11,539 (13.1%)
Three times or more	153,884 (1.3%)	587 (15.1%)	15,757 (17.9%)
Outpatient physician visits, past year			
0-1 times	4,054,472 (34.3%)	313 (8.1%)	10,673 (12.1%)
2-4 times	3,111,063 (26.3%)	608 (15.7%)	13,598 (15.4%)
5-8 times	2,320,703 (19.6%)	882 (22.7%)	16,897 (19.2%)
9-14 times	1,429,868 (12.1%)	926 (23.9%)	18,545 (21.0%)
15 times or more	894,149 (7.6%)	1,151 (29.7%)	28,394 (32.2%)
Income quintile (1= Highest)[m,n]			
1	2,351,451 (19.9%)	479 (12.3%)	14,152 (16.1%)
2	2,343,768 (19.8%)	552 (14.2%)	14,613 (16.6%)
3	2,364,379 (20.0%)	776 (20.0%)	17,011 (19.3%)
4	2,337,045 (19.8%)	933 (24.0%)	19,418 (22.0%)
5	2,301,617 (19.5%)	1,120 (28.9%)	22,469 (25.5%)
Missing	111,995 (0.9%)	20 (0.5%)	444 (0.5%)
Educational attainment quintile (1=Highest)[m,o]			
1	2,490,287 (21.1%)	638 (16.4%)	14,904 (16.9%)
2	2,513,154 (21.3%)	781 (20.1%)	17,337 (19.7%)
3	2,443,398 (20.7%)	729 (18.8%)	17,755 (20.2%)
4	2,260,406 (19.1%)	846 (21.8%)	19,110 (21.7%)
5	1,970,234 (16.7%)	852 (22.0%)	18,328 (20.8%)
Missing	132,776 (1.1%)	34 (0.9%)	673 (0.8%)
Proportion essential workers quintile (1=Lowest)[m,p]			
1	2,533,697 (21.5%)	705 (18.2%)	14,830 (16.8%)
2	2,592,332 (21.9%)	780 (20.1%)	17,367 (19.7%)
3	2,315,922 (19.6%)	760 (19.6%)	18,453 (20.9%)
4	2,217,021 (18.8%)	794 (20.5%)	18,163 (20.6%)
5	2,018,450 (17.1%)	807 (20.8%)	18,620 (21.1%)
Missing	132,833 (1.1%)	34 (0.9%)	674 (0.8%)
Proportion racially-minoritised groups quintile(1=Lowest)[m,q]			
1	1,826,634 (15.5%)	260 (6.7%)	18,046 (20.5%)
2	1,954,891 (16.6%)	454 (11.7%)	18,424 (20.9%)

3	2,105,986 (17.8%)	666 (17.2%)	17,568 (19.9%)
4	2,564,575 (21.7%)	964 (24.8%)	16,729 (19.0%)
5	3,225,565 (27.3%)	1,502 (38.7%)	16,672 (18.9%)
Missing	132,604 (1.1%)	34 (0.9%)	668 (0.8%)
Proportion recent immigrants (1=Lowest)[m,r]			
1	5,983,539 (50.7%)	1,499 (38.6%)	52,336 (59.4%)
2	2,412,998 (20.4%)	880 (22.7%)	16,208 (18.4%)
3	3,236,805 (27.4%)	1,464 (37.7%)	18,402 (20.9%)
Missing	176,913 (1.5%)	37 (1.0%)	1,161 (1.3%)
Proportion apartment buildings (1=Lowest)[m,s]			
1	6,605,697 (55.9%)	1,613 (41.6%)	42,666 (48.4%)
2	2,120,840 (18.0%)	687 (17.7%)	18,576 (21.1%)
3	2,944,390 (24.9%)	1,545 (39.8%)	26,093 (29.6%)
Missing	139,328 (1.2%)	35 (0.9%)	772 (0.9%)
Average household size quintile (1=Lowest)[m,t]			
1	2,325,763 (19.7%)	1,028 (26.5%)	25,171 (28.6%)
2	2,064,823 (17.5%)	571 (14.7%)	19,138 (21.7%)
3	1,582,415 (13.4%)	405 (10.4%)	12,471 (14.2%)
4	2,722,878 (23.1%)	861 (22.2%)	17,930 (20.4%)
5	2,975,277 (25.2%)	980 (25.3%)	12,625 (14.3%)
Missing	139,099 (1.2%)	35 (0.9%)	772 (0.9%)
Proportion high-density housing (1=Lowest)[m,u]			
1	3,983,354 (33.7%)	1,018 (26.2%)	31,975 (36.3%)
2	2,559,526 (21.7%)	675 (17.4%)	20,016 (22.7%)
3	2,289,131 (19.4%)	722 (18.6%)	15,862 (18.0%)
4	2,679,342 (22.7%)	1,370 (35.3%)	17,732 (20.1%)
Missing	298,902 (2.5%)	95 (2.4%)	2,522 (2.9%)

*Databases used for creation of individual-level characteristics included: Discharge Abstract Database, National Ambulatory Care Reporting System, Ontario Health Insurance Plan provider billings, Ontario Drug Benefits Plan, Continuing Care Reporting System, Canadian Organ Replacement Registry, and the Ontario Cancer Registry;

[a]Death within 30 days following or 7 days prior to a lab-confirmed positive COVID-19 test;

[b]Death without a lab-confirmed positive COVID-19 test; we did not include those who died more than 7 days prior or 30 days after a positive COVID-19 test in our definition of non-COVID-19 death, as we aimed to determine patterns of mortality by area-level SDOH without COVID-19 in our secondary outcome, limiting the assessment of the potential longer term impact of COVID-19 on the outcome;

[c]Age as of Mar 1, 2020;

[d]We defined rural as being located outside the commuting zone of a city with a population greater than 10000(29);

[e]The look-back window for comorbidities was since year 1991, unless otherwise specified;

[f] Frailty score >15 in the last 5-year;

[g]Treatment in last 6 months or diagnosis in last year;

[h]Diagnosis in the last 5-year;

[i]Immunocompromised defined as diagnosed with HIV (regardless of CD4 count) between 1991 till present, or had an organ or bone marrow transplant, or had another immunodeficient condition in the last 20 years;

[j]Advanced liver diseases defined as diagnosis of cirrhosis or decompensated cirrhosis;

[k]Diagnosis in last 5 years or had a procedure in last 20 years;

[l]Inpatient diagnosis in the last 20 years;

[m]Area-level variables at the level of the Census Dissemination Area

[n]Income quintile has variable cut-of values in each city or Census area, to take cost of living into account; a Census Disseminaton Area being in quintile 1 means it is among the highest 20% of dissenmination areas in its city by median household income;

[o]1st quintile represents areas with 0-4.1% of people aged 25–64 years without a diploma; 2nd quintile, 4.1-7.5% of people; 3rd quintle, 7.5%–11.4% of people; 4th quintile, 11.4-17.1% of people; and 5th quintile, 17.1-94.3% of people;

[p]1st quintile represents 0%–32.5% of working people in the area who self-identified as working in an essential job, including sales, trades, manufacturing, and agriculture; 2nd quintile, 32.5%–42.3% of people; 3rd quintile, 42.3%–49.8% of people; 4th quintile, 50.0%–57.5% of people; and 5th quintile, 57.5%–114.3% of people;

[q]1st quintile represents 0%–2.2% of people in the area who self-identified as racially-minoritised groups; 2nd quintile, 2.2%–7.5% of people; 3rd quintile: 7.5%–18.7% of people; 4th quintile, 18.7%–43.5% of people; and 5th quintile, 43.5%–100% of people;

[r]1st category represents 0%–2.1% of people in the area being recent immigrants who came to Canada within the last 5 years; 2nd category, 2.1%–4.7% of people; and 3rd category, 4.7%–41.2% of people; the high frequency of zeros permitted the creation of only 3 categories (i.e., the lower 3 quintiles combined, and the fourth and fifth quintiles);

[s]1st category, 0%–7.3% of buildings in the area are apartment buildings; 2nd category, 7.4%–37.7% are apartment buildings; and 3rd category, 37.7%–100% are apartment buildings; the high frequency of zeros permitted the creation of only 3 categories (i.e., the lower 3 quintiles combined, and the fourth and fifth quintiles);

[t]1st quintile represents 0–2.1 people/dwelling; 2nd quintile, 2.2–2.4 people/dwelling; 3rd quintile, 2.5–2.6 people/dwelling; 4th quintile, 2.7–3 people/dwelling; and 5th quintile, 3.1–5.7 people/dwelling;

[u]1st category represents 0–2.6% of households are considered high-density housing; 2nd category, 2.7-5.2%; 3rd category, 5.3-8.7%; 4th category, >8.7%; the high frequency of zeros permitted the creation of only 4 categories (the lower 2 quintiles combined);

'housing density'/'housing suitability' refers to whether a private household is living in suitable accommodations according to the National Occupancy Standard; that is, whether the dwelling has enough bedrooms for the size and composition of the household. A household is deemed to be living in suitable accommodations (non-high-density housing) if its dwelling has enough bedrooms, as calculated using the National Occupancy Standard.

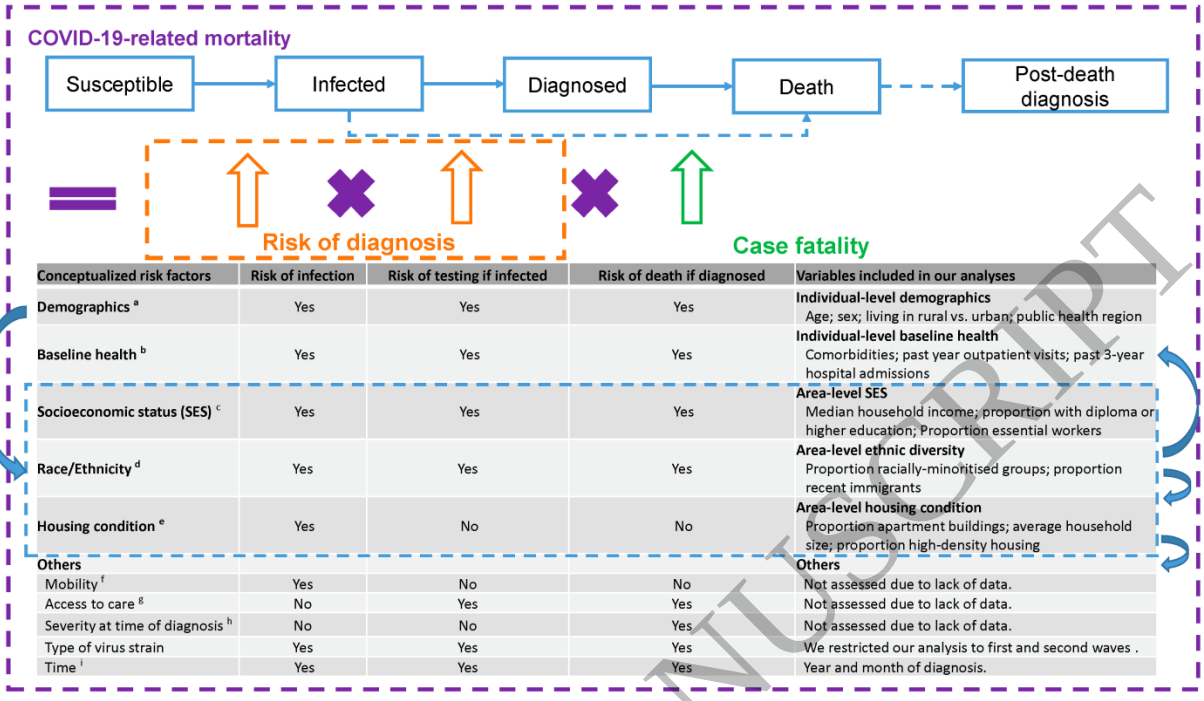
FIGURE LEGENDS:

Figure 1. Conceptualization of risk factors for COVID-19-related mortality. Based on the conceptualized factors, we sourced data where available, at individual-level, otherwise at area-level. [a]Areas where an individual resides might reflect contact rates in communities and health care system capacity and quality; and therefore associated with risk of infection, testing and death(1, 2, 12);[b]Individual's baseline health (e.g., comorbidities) have been correlated with susceptibility to COVID-19 infection, and severity of infection and therefore associated with risk of infection, testing and death(4);[c]Occupation (e.g., essential workers) might reflect contact rates at work and therefore be associated with risk of infection and testing (12, 55). Income and education, might affect exposure to the virus through working or living conditions, while also reflecting access to healthcare services, and therefore be associated with risk of infection, testing and death(12, 56);[d]Marginalized racial groups might be subject to systemic racism and socioeconomic inequalities, and affecting the risk pathway of COVID-19 related mortality(3, 8); [e]Housing conditions might reflect contact rates within household and be associated with risk of infection(12, 28, 57); [f]We assume mobility is a mediator for the relationship between SDOH and risk of infection; [g]We assume access to care is a mediator for the relationship between SDOH and risk of testing and death;[h] We assume severity at time of diagnosis is a mediator for the relationship between SDOH and risk of death; [i]There was a change occurred in August 2020 regarding clinical practice with respect to the use of steroids to treat COVID-19.

Figure 2. Associations between area-level social determinants of health (SDOH) and COVID-19-related mortality among community dwelling adult populations aged 20 years and older in Ontario, Canada between March 1, 2020 and Mar 2, 2021, with serial adjustment of potential confounders. Cause-specific hazard models were used for COVID-19-related mortality analyses. COVID-19-related death defined as death within 30 days following or 7 days prior to a positive COVID-19 test. Other demographics variables included whether individuals reside in rural vs. urban area, and the public health region where individuals reside. Baseline health variables included comorbidities (list in **Table 1**), number of hospital admissions in the past 3 years, and outpatient physician visits in the past year. Other SDOH variables are shown in the figure per Y-axis. All area-level SDOH variables are measured at the level of the Census Dissemination Area, except income (at census metropolitan area), and detailed definitions of these variables are shown in **Table 1** footnotes.

Figure 3. Comparing area-level social determinants of health (SDOH) in COVID-19-related mortality, non-COVID-19 mortality, and COVID-19 case fatality among community dwelling adult populations aged 20 years and older in Ontario, Canada, March 1 2020 – Mar 2, 2021. Multivariable cause-specific hazard models and logistic regression model were used to estimate cause-specific mortalities and case fatality, respectively. Death within 30 days following or 7 days prior to a positive COVID-19 test was considered in calculations of COVID-19 case fatality and COVID-19-related mortality. Death without a positive COVID-19 test was considered non-COVID-19 mortality. Demographics variables included age, sex, whether individuals reside in rural vs. urban area, and the public health region where individuals reside. Baseline health variables included comorbidities (list in **Table 1**), number of hospital admissions in the past 3 years, and outpatient physician visits in the past year. Other SDOH variables are shown per Y-axis. All area-level SDOH variables are measured at Census Dissemination Area level except income (at census metropolitan area), and detailed definitions of these variables are shown in **Table 1** footnotes. The case fatality model additionally adjusted for month of COVID-19 test.

Figure 4. Adjusted cumulative incidence function of COVID-19-related mortality by area-level social determinants of health (SDOH) among community dwelling adult populations aged 20 years and older in Ontario, Canada, March 1 2020 – Mar 2, 2021. Death within 30 days following or 7 days prior to a positive COVID-19 test was considered COVID-19-related. Estimates were obtained from the fitted Fine & Gray subdistribution hazard models. The models adjusted for demographics (age, sex, whether individuals reside in rural vs. urban area, the public health region where individuals reside), and baseline health (comorbidities (list in **Table 1**), number of hospital admissions in the past 3 years, and outpatient physician visits in the past year). Most at risk groups were defined as the SDOH level with the worst outcome; e.g., lowest income quintile; least vulnertable groups were defined as the SDOH level with the best outcome; e.g., highest income quintile.*Areas with medium level (quintile 3) average household size had the lowest COVID-19-related mortality and was defined as the least at risk group.



Conceptualized risk factors	Risk of infection	Risk of testing if infected	Risk of death if diagnosed	Variables included in our analyses
Demographics [a]	Yes	Yes	Yes	**Individual-level demographics** Age; sex; living in rural vs. urban; public health region
Baseline health [b]	Yes	Yes	Yes	**Individual-level baseline health** Comorbidities; past year outpatient visits; past 3-year hospital admissions
Socioeconomic status (SES) [c]	Yes	Yes	Yes	**Area-level SES** Median household income; proportion with diploma or higher education; Proportion essential workers
Race/Ethnicity [d]	Yes	Yes	Yes	**Area-level ethnic diversity** Proportion racially-minoritised groups; proportion recent immigrants
Housing condition [e]	Yes	No	No	**Area-level housing condition** Proportion apartment buildings; average household size; proportion high-density housing
Others				Others
Mobility [f]	Yes	No	No	Not assessed due to lack of data.
Access to care [g]	No	Yes	Yes	Not assessed due to lack of data.
Severity at time of diagnosis [h]	No	No	Yes	Not assessed due to lack of data.
Type of virus strain	Yes	Yes	Yes	We restricted our analysis to first and second waves .
Time [i]	Yes	Yes	Yes	Year and month of diagnosis.

Figure 1
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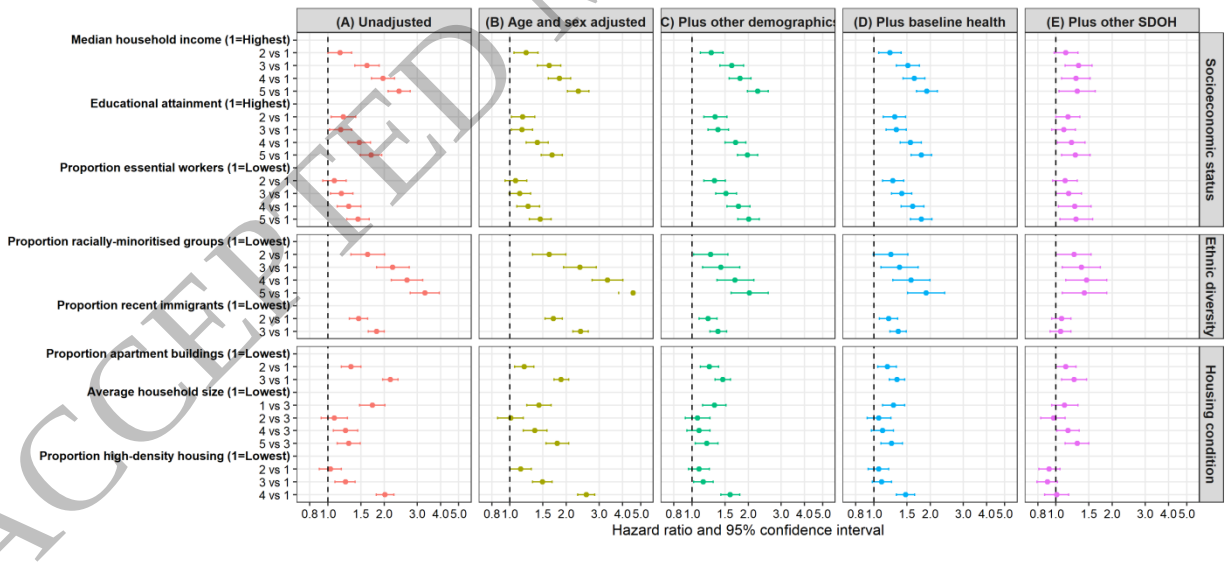

Figure 2
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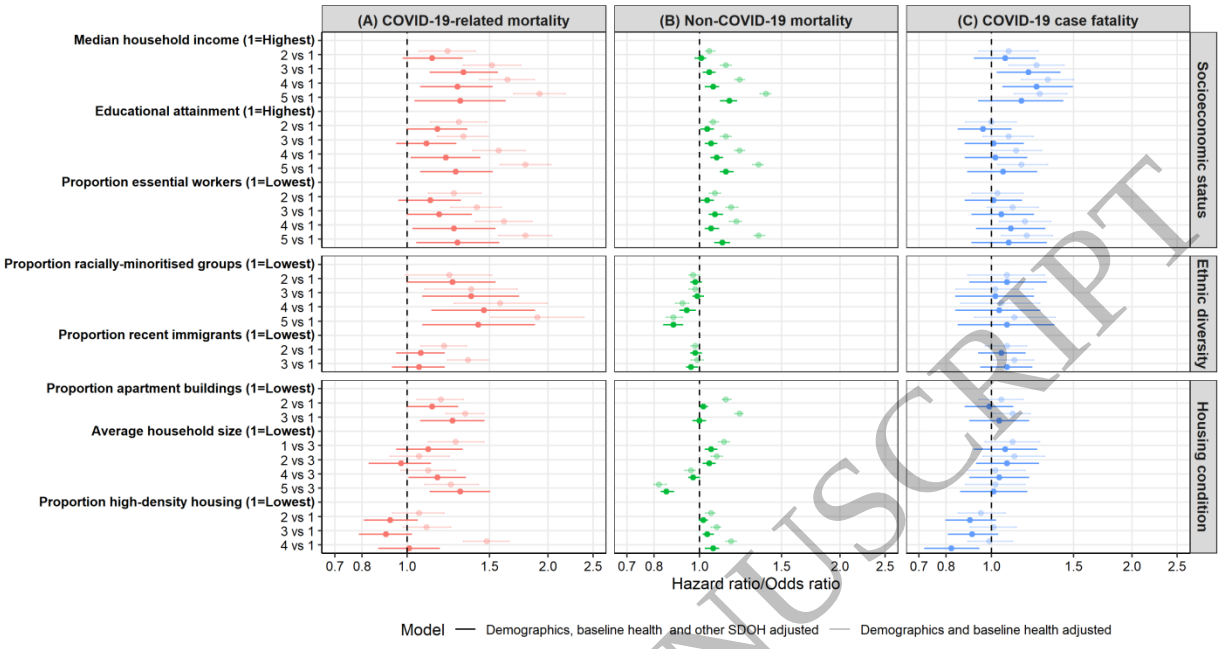

Figure 3

300x165 mm (x DPI)

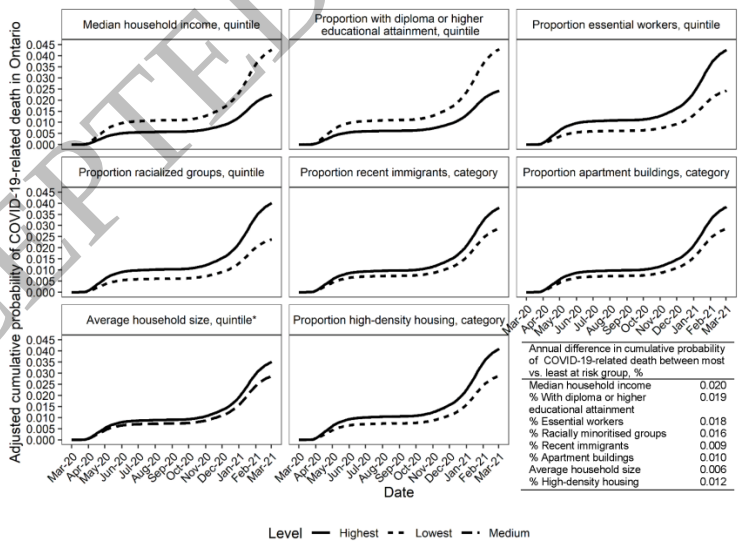

Figure 4
279x216 mm (x DPI)