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Title: Sporadic COVID-19 cases at the neighbourhood-level in Toronto, Ontario, 2020: a spatial analysis of the early pandemic period
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Reviewer 1: Dr. Jonathan Simkin
Institution: The University of British Columbia School of Population and Public Health, BC Cancer Agency
General comments (author response in bold)

Thank you for the opportunity to review this article. The article is very well-written, concise and topical. It would certainly be of great interest to the journal's readership. The methods were appropriate and robust, and I appreciate the work focusing at the small area level and accounting for spatial dependence. Small area analyses are valuable for public health surveillance and planning. There are some minor edits that I recommend and limitations to consider. Great job!

Abstract
1. With space permitting, consider adding the effect sizes and confidence intervals for the significant predictors.
Thank you for this suggestion. We have now updated the abstract to include the relative risks and their 95% confidence intervals (lines 31-32).

Methods
2. Consider adding the range for neighbourhood area and population size e.g. neighbourhood area ranged by # km to #km… population size ranged between …
Again, this is an excellent suggestion. We have included an updated table in the appendix to give more detail information about the neighbourhoods.

3. Was there a reason for the 1.5 SMR threshold? As opposed to say 2.0? I don't see a problem here, I'm just wondering if this was based on the expert opinion, clinical/real-world significance, or from cluster detection literature. Depending on the true size of excess risk, different methods have different capabilities of truly detecting a cluster. I think cluster at 1.5 or higher would be appropriately captured (vs. a lower SMR like 1.25). Here's a paper that could potentially support this decision: A simulation study of three methods for detecting disease clusters (Aamodt et al., 2006). Also, consider stating whether this was an a priori or post hoc criteria.
Thank you for this comment and for the suggested citation. We have included the citation you are suggested into the methods section to support our decision for the threshold that we used as the cut-off (lines 117-125).
"P-values to determine significance of the spatial scan test were estimated using 999 Monte Carlo simulations, where the null hypothesis is that the rate of cases within a cluster does not differ from the rate outside of the cluster. The SMR was calculated by dividing the observed cases by the expected cases calculated in the flexibly shaped spatial scan test (Tango & Takahashi, 2005). We excluded clusters where the lower bound of the SMR 95% confidence interval was below 1.5, as spatial scan tests are most suitable to detect clusters with relative risk of 1.5 and above (Aamodt et al., 2006). Additionally, it was determined that a SMR above 1.5 would be of public health interest. Therefore, we excluded clusters with a SMR 95% confidence interval that was lower than 1.5."

4. For the neighbourhood population data (rate denominator), what period do these reflect? Is it specifically the period under analysis or did you take the full 2020 year? Or most recent census data (2016)?
I have updated and provided a reference. Population estimates were from the most recent Toronto neighbourhood profiles which were based off of 2016 census data, I have included the reference to clarify this (line 78).

5. Similar question for the covariate data – what period is reflected for the covariate data?
The covariate data was from the same source – 2016 Toronto neighbourhood profiles, this was also clarified on line 79.

Discussion
6. Page 8 Line 22-29. If the model unit was neighbourhood level, I am wondering if the inclusion "individuals" in the statement of risk should be revised. Instead of

"there is a 3.67 times higher risk for individuals living in the area with the highest LIM-AT prevalence",

should the interpretation not be something like…

"The risk of sporadic COVID-19 cases was 3.67 times higher for the highest LIM-AT area compared to the lowest LIM-AT area".

As opposed to attributing the neighbourhood level risk to the individuals? I could be overthinking this, I'll leave it to you to consider.
Thank you for this suggestion, while I understand the rationale behind your interpretation, I believe that it is the individual that should be considered here since the location of where an infection is acquired is not known. The infection could be contracted outside of the area where they live – attributing the increased risk to the area would be incorrect in this circumstance, there is an increased risk to individuals that live within the area.

7. Page 16 line 4-6; I suggest adding "at the neighbourhood level" to the sentence given different contexts/scales of spatial variation for COVID19 pandemic.
Unfortunately, it is unclear which sentence this is referring to since the manuscript does not have 16 pages. However, I believe it may have been referring to page 9 and I have updated the paragraph as follows (lines 209-218).
"The GLGM found that average household size and LIM-AT prevalence were associated with the rate of sporadic COVID-19 at the neighbourhood level (Table 2). For average household size, when the average household size in a neighbourhood increased by 1, the risk of sporadic COVID-19 increased by a factor of 2.17. Additionally, as the percentage of households that fall within the low-income measure criteria increased by 1%, the risk of sporadic COVID-19 cases increased by a factor of 1.03, at the neighbourhood level. Considering the difference between the neighbourhoods with lowest LIM-AT prevalence (4.5%) and the neighbourhoods with the highest prevalence (45.5%), there is a 3.67 times higher risk of sporadic COVID-19 for individuals living in the area with the highest LIM-AT prevalence."

8. Limitations

o I recommend acknowledging that there are other options besides queen's to define the relationship between areas and measure/account for spatial dependence, such as KNN matrix.

Thank you for the comment. We have decided not to include additional text outlining alternative spatial structures, to keep within the word count of the journal.

o Were there other potential confounders that weren't available/not accounted for? Such as proportion of recent immigrants vs. long term residents? Visible minorities, Indigenous peoples and/or BIPOC populations? Education? Walkability scores or land use type measures?

Thank you for the suggestion. There are a wide variety of variables that could have been considered and we only selected a subset of those. I have added some notes to the limitations to reflect this fact (lines 254-257).

"First, we are only looking at a limited set of group-level factors and summary values. This does not often give the full picture and may miss individual variation, such as specific sex, age, race differences, and additional variables may be of interest in future studies."

o I recommend acknowledging the modifiable area unit problem and that further analyses at different scales should be considered.

This is a great suggestion and is definitely important for any geostatistical analyses. I have updated the limitations to reflect this (lines 262-267).

"Additionally, when interpreting spatial studies, it is always important to consider the modifiable areal unit problem (MAUP) that occurs when studies aggregate spatial data to regions. The level of aggregation selected, in this study the neighbourhood level, effects the interpretation of the findings, as results may vary if another level of aggregation was selected (such as census tract or dissemination area)."

o Consider acknowledging other methods that can be used to identify areas with excess risk, such as local indicators of spatial autocorrelation (LISA) and Bayesian hierarchical modelling approaches.

Thank you for the comment. We have decided not to include additional text outlining alternative modelling approaches, in order to keep within the word limit for the journal.

o Similar to a comment before on the SMR at 1.5, but consider a comment on the sensitivity of SatScan method to detect clusters.

Thank you for the comment, I have added a line in the limitations to discuss that the spatial scan tested used can only detect small clusters (lines 267-269).

"The flexibly shaped spatial scan test has limitations including being most practical for detection of small clusters and if larger clusters wanted to be considered, alternative methods would need to be used (Tango & Takahashi, 2005)."

Reviewer 2: Jane Law
Institution: University of Waterloo
General comments (author response in bold)

Thank you for the study that I found interesting to read.

1. Page 4 under data sources:
Could you explain why that subset of covariates was selected? See, for example, https://toronto.webex.com/webappng/sites/toronto/recording/28b69f1143d343efb4fe2ae6599661bd/playback (June 4, 2020). Risk factors include lower income, lower education, unemployment, newcomers, racialized groups, and sales and trades.
Thank you for this comment. We selected variables that are a subset of those used to construct the Ontario Marginalization Index. We did also conduct an analysis that included the percentage visible minority (a variable included in the neighbourhood profiles) however it was found to be not significant and was removed from the final model. This has been noted in the updated paper in the methods and results sections. This section (lines 136-148 and lines 181-189) now reads,
"To account for spatial autocorrelation, a generalized linear geostatistical model (GLGM) was fit to model the effect of average household size, population density, LIM-AT, percentage visible minority, and dependency ratio on the number of sporadic COVID-19 cases at the neighbourhood level with population as the offset."
"A GLGM was fit and there was a significant effect of household size, and percentage of low-income households (defined by LIM-AT) on risk of sporadic COVID-19 cases. Population density, percentage visible minority, and the dependency ratio were not significant in the model and were removed. The final GLGM, including only average household size and percentage of low-income households, found both variables to be significant (Table 2)."

2. Why not use the marginalization index or its domains directly? Explain its disadvantages over your set of covariates.
Thank you for this comment, the marginalization index is not available at this geographic level of aggregation, and to do so would require manually recreating it from census variables at the alternate geographic scale. Instead, we selected some of the variables that are used in the index to create our model.

3. Have you considered standardizing the ratio by age groups instead of 15-64 (one group only)? Please explain
Thank you for this comment. We did not have the case data broken down by age group at the neighbourhood level and therefore were unable to do any forms of standardization. We did consider including the proportions of individuals within each age group by neighbourhood in the model, however the variables were highly correlated.

4. Have you considered controlling for or explain how you have controlled for
i. age group when seniors are more vulnerable,
ii. high rates or clusters in long term care homes,
iii. high rates or clusters in retirement homes (given that data of these homes are available)
Why not? Discuss how this could impact the results of clusters and risk factors.
Thank you for this comment.
i. The dependency ratio variable would in part account for age of seniors since they would be considered dependents (outside of the working age group). It

would require us to change this variable for some other age structure to account for this separately which we did not do.

ii. Outbreaks in long term care homes would not be considered in this analysis due to selecting only sporadic cases, this was intentional to examine dynamics on a community level opposed to outbreaks. This has been clarified in the methods section (lines 70-72).

"To explore the dynamics of spread at the community level, sporadic cases were selected, and outbreak related cases were excluded. The definition of sporadic cases is "all cases not linked to an outbreak in general members of the population" (Toronto Public Health, 2020)."

iii. The comment for (ii) regarding LTCH applies here to retirement homes as well, they would be included under outbreaks and are not included in this analysis.

5. Ref 7: Could you provide a link?

Yes, sorry for this oversight. A link has now been added to the reference list.

6. Page 5: Please explain briefly what "flexible" means for the spatial scan test? Briefly describe how the method works. For identifying clusters, local Moran's I and Kulldorff's scan test were commonly used. Have you considered using these methods? Why were they not used? Explain why the selected methods were used. What are the advantages of your method over them? A more thorough literature review of the approaches and methods used to identify clusters and risk factors for the infectious disease should be helpful.

These are all great considerations, and it is true there are multiple methods for identifying clusters. We have updated the methods to provide a more in-depth justification for the use of the flexibly shaped spatial scan test (lines 103-116)

"The flexibly spatial scan test was selected as it allows for irregularly shaped clusters to be detected that would not be picked up by more traditional methods (i.e., circular scanning window). The spatial scan test identifies clusters by gradually scanning each neighbourhood and increasing the scanning window to a maximum cluster size. The window that attains the maximum likelihood is identified as the primary, most likely, cluster. Additional clusters may then be identified. The maximum number of regions in a cluster was set to 14 as this represented 10% of neighbourhoods and the respective population would be still below the maximum size of 50% of total population for a single disease cluster. Identifying small clusters are preferred for public health studies to allow for intervention to be applied more easily, and clusters larger than 10-15% of the total regions are unlikely (Tango & Takahashi, 2005)."

7. Page 5: Briefly explain why UTM 17N projection was applied.

I have updated the sentence in the methods regarding the UTM 17N projection to explain that UTM 17N was done to minimize distortion in the maps (line 98).

8. Page 6: Generalized linear geostatistical model used. Briefly explain how the method works. Have you considered using spatial regression that has been commonly used for identifying risk factors? Explain why you chose the GLGM method. Discuss its advantages and disadvantages over the spatial regression method.

Thank you for your insight. It is true that there are multiple ways to model spatial data and there are advantages and disadvantages to each. In order to keep our

manuscript within the journal word count we have not provided additional details about other methodologies that were not used in this paper.

9. Page 7:
-Moran's I and Geary's C tests indicated spatial clustering, so what? Explain your purpose in conducting these two tests. How does their result relate to your scan test results reported on page 7 regarding cluster location?
When updating the manuscript we chose to only include Moran's I test for spatial clustering as it is likely redundant to include both. The test is used to determine if there is spatial dependence in the data (which there was), indicating that we should consider a model that accounts for this (such as a GLGM).

10. Page 9:
Limitations:
Add discussions on the reliability of the results, how they could be impacted by, for example,
i. Individual variation missing. You also mentioned on page 9, first para., individual-level factors. How has this been tackled in the literature? What methods of analysis that involve individual-level factors did you have in mind? Discuss to help readers with future research!
Limitations – Thank you for these suggestions, I have included some additional details within the limitation section (lines 254-257)
"First, we are only looking at a limited set of group-level factors and summary values. This does not often give the full picture and may miss individual variation, such as specific sex, age, race differences, and additional variables may be of interest in future studies."

ii. Discuss how the missing postal code data might impact the results of hotspots and risk factors.
Thank you for this comment. Due to the low proportion of missing postal codes (703 out of 30,598 sporadic cases had missing postal codes, 2.3%), we do not expect this to have any meaningful impact on the results.

iii. Have you considered the modifiable areal unit problem and ecological bias? Briefly discuss.
Limitations – Thank you for these suggestions, I have included some additional details within the limitation section (lines 262-267)
"Additionally, when interpreting spatial studies, it is always important to consider the modifiable areal unit problem (MAUP) that occurs when studies aggregate spatial data to regions. The level of aggregation selected, in this study the neighbourhood level, effects the interpretation of the findings, as results may vary if another level of aggregation was selected (such as census tract or dissemination area)."

iv. Your study used a specific period of covid-19 data that are available since the pandemic began. Could you discuss how you would recommend an approach to determine the period(s) of covid-19 data to use for cluster detection for prioritizing vaccination, for instance?
Thank you for the comment. It is true that these methods could be used to prioritize vaccinations in hot spots, however determining a period of time for this

approach is beyond the scope of this project and would require additional research.

11. Page 13: Figure 2 - the yellow cluster looks to contain two parts. Explain how they should be interpreted. Also, would you be able to discuss how to interpret the relative importance of clusters 1, 2, and 3, according to the spatial scan method used or your thoughts?
The cluster should be interpreted of areas of excess risk as the rates within the clusters are higher than Toronto overall. I added some additional information in the interpretation section regarding this (lines 203-208).
"Three clusters of elevated risk of sporadic COVID-19 cases were found within Toronto neighbourhoods with SMRs ranging from 1.59–2.43 (Table 1; Figure 2). While Cluster 1 is identified as the most likely cluster through the spatial scan test, all clusters are of importance for public health considerations. These clusters can be identified as key areas to target additional COVID-19 resources towards, such as pop-up testing clinics or targeted areas for vaccination."

12. Could you be more specific on how the findings are relevant to combating covid-19. For example, currently, postal codes were used to prioritize areas for vaccination. Discuss how in practice, Toronto can make use of your findings to combat covid-19 better.
Thank you for this comment, I have added some comments regarding this in the interpretation and conclusion (lines 206-208, lines 232-234, lines 280-283).
"These clusters can be identified as key areas to target additional COVID-19 resources towards, such as pop-up testing clinics or targeted areas for vaccination."
"Policies are needed to address these risk factors and use information such as this to develop targeted strategies for vaccination."
"Policies such as paid sick days, hotel quarantine sites, and targeted vaccination strategies, could help close the gap in some of the inequalities identified in this study and could help prevent the spread of COVID-19."

Reviewer 3: Dr. Leonardo Azevedo
General comments (author response in bold)

Comments on manuscript 'Spatial analysis of sporadic COVID-19 cases at the neighbourhood-level in Toronto, Ontario, 2020.'

The manuscript deals with an interesting and important topic and attempts to correlate the number of sporadic covid-19 cases with socioeconomic variables. It combines spatial analysis and geostatistical regression. While the idea sounds good, and the results interesting, I think the manuscript lacks a description of the methodology and a deeper interpretation of the results. In the current form, the work presented is not reproducible. As I believe is just a matter of including more description in the manuscript. My main comments below.

1) Lack of description on how sporadic cases were defined, or selected, from the dataset. Were they available from the datasets? This is important as the authors mention the interpretation might be biased.

Sporadic cases were defined by the technical notes of the Toronto Public Health dashboard and the definition was updated and a reference was provided (lines 67-69).
"A case is defined as a confirmed or probable case of COVID-19 reported to Toronto Public Health through the Public Health Case and Contact Management Solution (CCM) (Toronto Public Health, 2020)."

2) It would be good to have an idea of the population size of each neighborhood, so check for low population sizes.
This is a great point, I have added an additional table in an appendix that provides summary measures for the neighbourhoods (Appendix Table 1).

3) Not clear what Bayesian smoothed rates produces on the original incidence rates per neighborhood. Is this method applied to overcome the small population sizes? If so, besides the description of the min and max ranges you should show the differences on the maps.
Empirical Bayesian smoothing is used to reduce "sampling error" and as a form of standardization. The idea is to standardize the rates against varying sample sizes to make rate estimates more comparable between regions. I have included both the raw and smoothed rates in the summary table in the appendix (Appendix table 1).

4) No description of what is flexible scan test.
I have updated the methods to explain the flexibly shaped spatial scan test (lines101-119).
"A flexibly spatial scan test was used to determine the locations of probable geographic clusters of elevated sporadic COVID-19 rates and estimate the standardized morbidity ratio (SMR) within identified clusters (Tango & Takahashi, 2005). The flexibly spatial scan test was selected as it allows for irregularly shaped clusters to be detected that would not be picked up by more traditional methods (i.e., circular scanning window). The spatial scan test identifies clusters by gradually scanning each neighbourhood and increasing the scanning window to a maximum cluster size. The window that attains the maximum likelihood is identified as the primary, most likely, cluster. Additional clusters may then be identified. The maximum number of regions in a cluster was set to 14 as this represented 10% of neighbourhoods and the respective population would be still below the maximum size of 50% of total population for a single disease cluster. Identifying small clusters are preferred for public health studies to allow for intervention to be applied more easily, and clusters larger than 10-15% of the total regions are unlikely (Tango & Takahashi, 2005). P-values to determine significance of the spatial scan test were estimated using 999 Monte Carlo simulations, where the null hypothesis is that the rate of cases within a cluster does not differ from the rate outside of the cluster."

5) It is not clear how the authors convert the incidence per 100,000ha into SMR
The SMR is calculated by dividing the observed cases/expected cases, provided by the output from the flexibly shaped spatial scan test (R package smerc) using the methods from Tango & Takashi, 2005 (lines 119-121).
"The SMR was calculated by dividing the observed cases by the expected cases calculated in the flexibly shaped spatial scan test (Tango & Takahashi, 2005)."

6) About the spatial correlation structure could you show the variogram models?
It is not typically the case that diagnostic plots and graphics are included in manuscripts (e.g. Q-Q plots etc.) We have chosen to not include further diagnostic graphics however, will defer to the journal publication norms in this regard.