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Title	**Temporal-spatial case-crossover analysis of the effect of air pollution on myocardial infarction**
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Reviewer 1	Dr. Paul D. Hasselback
Institution	Island Health, Medical Health Officer, Nanaimo, British Columbia
Reviewer comments and author response	This study adds to the growing body of evidence on small area spatial variation in exposure to pollutants being associated with an increase in health risks. The study is specific to only myocardial infarction (MI) and based on available detailed data on MI in the Calgary community. The authors are commended for the methodology and robustness of their approach. This is a strong research team and a strong paper. The critique that follows can hopefully contribute the quality of the final product while recognizing that at times, comments may seem trivial. Response: We want to personally thank Dr. Hasselback for providing thoughtful and informative comments to our manuscript. The revised manuscript is considerably improved as result of following the key suggestions from the editors and reviewers—thank you! Specific comments 1. Line 107 – while detailing the surveillance system, some measure of validity would be welcomed such as known to capture XX% of non-fatal events, and data completion on all variables of XX% Response: APPROACH data collection is prospective and collected by trained clinical staff using standardized operating procedures and data definitions as part of the medical record in Alberta, missing data on key variables are minimal. Data from APPROACH are routinely enhanced by merging the clinical registry data to administrative data records to supplement clinical information and enhance to diagnostic and prognostic validity of the registry. For example, missing data on diabetes status in the APPROACH registry has been only 6.6%. Because the registry serves as the clinical record in Alberta for cardiac catheterization reporting it is not possible to calculate a measure of validity for the registry as the registry data constitutes a clinical gold standard for MI diagnosis in Alberta. However, a comparison of the APPROACH Heart Alert registry to administrative data holdings from Alberta's hospital discharge abstract compared favorably with a 0.5% higher incidence of myocardial infarction in the Heart Alert registry (53.0%) versus the discharge abstract database (52.5%). 2. It may be important to indicate that fatal out of hospital events are not captured. While MIs are increased secondary to exposure to air pollution, the main cardiac component of fatality correlated with air pollution events is sudden death – and the discerning reader may be interested in what proportion of such events are never "admitted to the cardiology services". Presumably deaths in emergency department are not included. Please note, the authors have been explicit in detailing their method, however the reader would benefit from understanding the limitations.

	Response: Thank you for raising this important consideration. You are correct that fatal out of hospital events and death occurring in the ED department are not captured in the APPROACH database. We have confirmed this point in the methods and raised this as a limitation in our discussion. 3. This reviewer is unfamiliar with LUR modelling for the NO2 estimates and is not able to comment on the appropriateness of the modelling or its implications. Response: We appreciate your candor. Please note that co-investigators on this paper include the lead researchers who developed the LUR model in Calgary. The following reference provides considerable more information on the LUR model in Calgary: S Bertazzon, M Johnson, K Eccles, GG Kaplan. Accounting for spatial effects in land use regression for air pollution modelling. Spatial and Spatio-temporal Epidemiology. 2015 Oct; 14-15: 9-21. 4. Line 136 – while the study has alluded to using PM2.5 and PM10, reference is made to PM1.0 it would be suggested that if this is not a typo, the PM1.0 information is not applicable to this study and should not be included. Readers can reference back to the original LUR studies for Calgary to find such conclusions. I suspect most readers would not appreciate the difference between PM1.0 and PM10 Response: PM1.0 was a typo—we have corrected (i.e., PM10). We apologize for this error and appreciate your thoroughness in identifying this mistake. 5. I am of the impression that the entire city has been assigned a NO2 exposure level based on 6 digit postal codes. The authors refer to “neighbourhood” and this may be the terminology used for postal code area. Or an alternate interpretation is that some other measure of ‘neighbourhood’ was used and from previous studies, postal codes are assigned to the neighbourhood. Calgary does have specified “neighbourhood” geographies (eg https://en.wikipedia.org/wiki/List_of_neighbourhoods_in_Calgary). Response: We assigned individuals who experienced a myocardial infarction their spatial NO2 exposure based on their home residence as defined by six-digit postal code. We used the term ‘neighborhood’ to simplify the description/discussion of the residential linkage to spatial NO2 exposure. In the methods we are describe that spatial linkage is based on the six-digit postal code. 6. It is a minor point, however the reader will benefit from specificity of the definition. Response: As above we have revised the manuscript to be more precise that we meant linkage based on six-digit postal code. 7. One of the challenges for a research group that is so well endowed with strong statistical support, is converting such information into words that are more understandable for the audience they are reaching. The paper is written for an audience of experts in the measurement of air quality and health. The audience of CMAJ Open, while very knowledgeable and health oriented, is more predominately a less statistically oriented audience. The challenge can be put to the research group on how to present their findings in an accurate fashion, while not losing their

	audience in the plethora of statistical analysis and terminology. In this respect I believe the authors should reconsider what and how the data is presented. Response: This is a difficult request because the methodology applied (integrating temporal and spatial air pollution) is novel and thus, requires detailed information on the methodology and the limitations of our work. In fact, based on the editor's comments, we have only added to the statistical and methodological complexity of the paper. Nonetheless, we have carefully read over the paper and have revised the paper to stress key messages stemming from the data that we believe will be highly relevant to the broad audience of CMAJ Open. One potential solution to striking a balance between methodology and message is an editorial. If this paper is accepted by the editors of CMAJ Open, we hope they use your important comments to write an editorial on the paper. 8. Line 188 – I am unclear on the purpose of presenting distribution measures and correlation matrix. Of greater interest for air quality purposes would the proportion of time/measures exceeding some criterion level. Line 208 provides an indication of 1% of days with advisories, though does not provide for the basis on which advisories are issued (AQHI only, single pollutants, use of CAAQS?). I am not convinced any of this contributes to the paper, however as presented it does not add to the main research question and may detract from the study. Response: Thank you for raising these important points. The main purpose of including Appendix 1 (i.e., distribution of air pollutants and their correlation) is to provide a frame reference for air pollution exposure in Calgary. Air pollution exposure varies dramatically between cities across the world. By providing this information, investigators from other regions of the world can compare our results against air pollution levels in their cities. 9. Lines 198- 230– the authors have attempted to distinguish between the toxicological effects of specific pollutant exposures, and the general challenge of all air pollution research that routinely measured pollutants are part of a multipollutant mix and not necessarily the only contributors to health outcomes. They have been cautious to not suggest causality though avoid being explicit on this as a limitation. Response: You are entirely correct are associations are not causal. We have revised the limitation section of our manuscript to explicitly state that the findings of our study are not causal. 10. Line 236-238 – the potential confounders that may contribute to explanation are important to highlight and it is appreciated that the authors note they have not attempted to adjust for socioeconomic status (although SES may also explain choice of residence which may increase likelihood of exposure). It is appreciated that note is made of the complexity of attempting to parse out the contribution of specific pollutant exposure. Response: The editors raised this point as well. As per our response above: The case crossover study design (i.e., temporal association) controls for non-time varying exposures such as socioeconomic status and obesity because the case serves as their own control and during the risk set (same day of the week, month, and year as the event) an individual's BMI and socioeconomic status will not vary greatly. However, our spatial analysis that stratifies an individual home residence into low, intermediate or high exposure to NO2 (as defined by the land use

	regression model) is subject to confounding. For example, an individual with low socioeconomic status may live in a neighborhood in close proximity to highways (i.e., higher air pollution exposure) because these neighborhood have lower property values. We have expanded on this limitation in our discussion. 11. Line 239 – note is made of the potential for statistical associations being attributed to multiple comparisons, in this study the lack of independence of some of the results and collinearity (if any) associated with lag measurements should also be mentioned. Response: Multiple comparison error is possible with our study because each air pollutant and each lag period represents a separate conditional logistic regression model. For example, in Table 2, we analyze six air pollutants and the AQHI using five different lag periods—each odds ratio with 95% CI represents a separate conditional logistic regression model adjusted for temperature and humidity. We have added to our discussion the potential limitation associated with lack of independence and collinearity. Table 2 12. Odds ratio precision to three decimal points is not likely statistically appropriate (based on CI ranges), but more important is unnecessary. It is this sort of presentation that contributes to a seas of potential numeric confusion. Response: We apologize for the confusing presentation of our data. We have revised all results to only include two decimal points. 13. While index day, lags and averages are appropriate to have explored, the results are not all independent – something that is not readily interpretable from Table 2. Pollutant specific lags are often correlated and we have no measures of correlation or interdependence. Response: As above, we have included the potential correlation/interdependence as limitations in our discussion. 14. Figure 1 – those unfamiliar with Calgary would not necessarily interpret white areas as regions of no residents (eg. parkland) – and there would also appear to be some areas that are relatively uninhabited (?farmland) that have not been classified relative to air pollution tertile. I may be speculating, but do the centroid circle points represent a minimum population for a particular postal code? Response: As we do not have geographic data on the shape and size of postal codes, we use centroid point of each postal code to represent the area covered by that postal code. All the centroid points have the same size of dot symbol. The shades of color represent the level of air pollution estimated in the postal code. The white areas include two different types of areas: 1. Areas without residents such as Elbow River, Bow River and Glenmore reservoir. There is no postal codes assigned to such areas. 2. Areas with assigned postal codes but the use of centroid points lead to white spaces between the two neighboring centroid points. As long as a postal code is assigned, the air pollution level in that postal code is included for analysis. To help clarify, we added to the legend of the figure the line used for the border and called it "limit of populated area". Also, we added a layer with parks and major water bodies and coloured them that they stand out; this has also been added it to

	the legend. Thank you for the opportunity of reviewing. This is a valuable contribution to the understanding of air pollution impacts on health and spatial variation in risk. Response: We thank you again for your insightful and informative feedback.
Reviewer 2	Dr. S Doerken
Institution	Freiburg, Germany
Reviewer comments and author response	Overall, the reporting of the study and the results is well done. A strength of the study is that different control periods were used in the case crossover analysis. Response: We want to personally thank Dr. Doerken for providing thoughtful and informative comments to our manuscript. The revised manuscript is considerably improved as result of following the key suggestions from the editors and reviewers – thank you! Methods: 1) Figure 1: The legend states that the area was stratified which in my mind implies a "splitting" of the area. Since I believe that stratification refers to the colored dots, maybe "mapping" of the area would be an appropriate term. Response: We apologize for the lack of clarity in the figure and figure legend. The figure represents the spatial distribution of NO2 in Calgary based on land use regression (LUR) model estimates. The LUR was used to stratify the NO2 concentrations into three levels: low, medium and high concentrations. Each 6-digit postal code is assigned one of the three NO2 concentration strata. The dots represent the centroid of each six-digit postal code in the City of Calgary. Next, we linked the residential six digit postal code of each patient who had a MI to one of the three strata. We have revised the figure legend to improve its clarity. 2) "MI patients were assigned to each of the three areas based on the six-digit postal codes of their residential locations": Figure 1 implies that postal codes include more than just one of the low/medium/high strata. How was this handled, i.e. how was a patient assigned to a single stratum? Response: Each six-digit postal code belongs to only one strata. Due to the scale of the figure, the dots overlap. However, their position on the map corresponds to the centroid of the six-digit postal code. To confirm, each patient with a MI are assigned only value for NO2 concentration (i.e. either high, medium, or low). We have added this point to the methods. 3) The case crossover design is best suited for studying outcomes that are acutely triggered by an exposure. Please describe if this is a valid assumption for the exposure-outcome relationship here. Response: The editors asked us a similar question, we have copied our response below: Response: A time-stratified case-crossover study design is widely used to evaluate associations between an acute exposure and the acute onset of a disease. The study design for air pollution research is well described in the following publication (Schwartz J. The effects of particulate air pollution on daily deaths: a multi-city

	case crossover analysis. Occup Environ Med. Dec 2004;61(12):956-961). This study design has been used to show a relationship between air pollution and myocardial infarction in prior studies (Nuvolone et al. Am J Epidemiol. 2011 Jul 1;174(1):63-71 and Peters et al. Circulation. 2001;103:2810-2815), as well as other health events such as stroke (Villeneuve et al. Sci Total Environ. Jul 15 2012;430:193-201), and asthma (Villeneuve et al. Environ Health. 2007;6:40). The design is appropriate because myocardial infarctions have abrupt onsets with a short latency period. This design is an adaptation of the case–control study in which cases serve as their own controls. The case's exposure at the ''index'' time (i.e., day of admission for myocardial infarction) is compared to their exposure at control time intervals, which are chosen using a time-stratified design. The time-stratified selection of periods occurs as follows: i. the index period is measured before the event; and, ii. the control period is measured before and after the event. The time-stratified approach matches the exposure (control to case intervals) by day of the week and month. For example, if the myocardial infarction occurs on the second Wednesday in the month of July of 2011, then the referent period will be the other Wednesdays in July of 2011. The reason that control intervals are chosen before and after the event is to control for seasonal patterns. Selecting a control date after an event occurs is acceptable because the effect of the event (i.e., myocardial infarction) does not influence air pollution levels. Navidi (Epidemiology. Jan 2002;13(1):100-105) provide greater elaboration on the need for using bidirectional control sampling in the case-crossover design. Overall, the rationale of using this study design is as follows: 1. The time-stratified case-crossover study design has been widely used to evaluate associations between acute air pollution exposure and acute health events such as myocardial infarction. 2. Because within-individual comparisons are being made, confounding from time-independent risk factors are controlled for by the design of the study. The case crossover study design has been shown to effectively control for confounders that are relatively stable in time. 3. The matching of control to case periods by day of week will control for the influence of day-of-week effects. However, sufficient variability is still left over in the air pollution exposures to evaluate associations. 4. The time-stratified design adjusts for seasonal trends in exposure levels. The time stratified approach is not subject to bias resulting from time trend because there is no pattern in the placement of referents relative to the index time. We have expanded the methods to explain the rationale for using a case crossover study design to assess the temporal association between acute (temporal) association of air pollution and the occurrence of myocardial infarction. We have also included a Figure that illustrates the study design. 4) I didn't fully understand the different control periods that were used. I understood that there are two controls periods, one before and one after the index period. Are they placed 7 days before/after to match the day of the week? What is a 1/2 day lag here? Response: The control periods are the other corresponding weekdays in the same month as the myocardial infarction. For example, if the myocardial infarction occurs on the second Wednesday in the month of July of 2011, then the referent period will be the other Wednesdays in July of 2011. A detailed review of the performance of several different strategies to select control intervals within a case-crossover design showed in simulation models that the time-stratified approach to select control intervals was the best method to select control periods. Please see

	the following paper for a comprehensive discussion: Janes et al. Case–Crossover Analyses of Air Pollution Exposure Data: Referent Selection Strategies and Their Implications for Bias. Epidemiology. Nov 2005;16(6):717-726 We have revised the methods of the paper to better explain the rational for using a time-stratified approach to select control intervals. In addition, we have created a figure that illustrates our study design—including the selection of control periods. We hope this figure will help the reader understand the complex study design. 1) Table 2: The odds ratios of the pollutants may not be meaningful in the presence of AQHI since the latter is a combination of the former, thereby adjusting for the pollutants twice. Consider using just one or the other. Response: The Air Quality Health Index (AQHI) is an information tool used in over 50 Canadian cities to inform the public about daily air quality and provide advice on how to limit short-term exposure to air pollution. The AQHI is a single composite score that is calculated from the combined pollutant levels of NO2, O3, and PM2.5. The score is based on a scale of 1 through 10 and stratified into different risk levels. The AQHI is calculated from a composition of 3-hour average values of O3, NO2, and PM2.5 based on this formula: AQHI =10/10.4*(100*(exp(0.000871*NO2)-1+exp(0.000537*O3)-1+exp(0.000487*PM2.5)-1)) Please note that each pollutant and the AQHI are modeled separately. In Table 2, the pollutants listed in the rows (O3, NO2, SO2, CO, PM10, and PM2.5) are each modeled separately. Only the last row in Table 2 is the AQHI (i.e., composition of O3, NO2, and PM2.5 based on the formula above), modeled separately. 2) An additional table could describe the mean values of the exposures in the index period and the control periods. However, I leave it up to the authors to decide this. Response: This table is not likely to be informative because case and control days differ among individuals such that any given calendar day could be a case day for one case and a control day for another case. Discussion: 1) Cross-over studies are prone to a carry-over effect, please discuss if this is possible here and if the washout period is appropriate. Response: Carry-over effect is not likely to be a factor in case crossover study design because the case serves as their own control and the control periods are temporal (i.e., different days in the month). For example, if the myocardial infarction occurs on the second Wednesday in the month of July of 2011, then the control periods will be the other Wednesdays in July of 2011. Air pollution levels on the second Wednesday in the month of July 2011 are compared to air pollution levels in the other Wednesdays (when the MI did not occur) in July 2011.