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Title	Regional health care services and rates of lower extremity amputation related to diabetes and peripheral artery disease: an ecological study
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Reviewer 1	Prof. Lynne Moore
Institution	Department of Social and Social and Preventive Medicine, Université Laval, Québec, Que.
General comments (author response in bold)	The authors present an ecological study to examine the correlation between regional health care services and rates of amputation in Ontarians >40 yo based on 10 years of population-based data through March 2017. It is an interesting study on an important topic with the potential to guide policy of healthcare infrastructure. I have several questions/suggestions: 1. Some information on the burden of amputations in the introduction (incidence, consequences, costs) would be useful. **Thank you. Within the limits of the word count, we mention a rising rate and now provide commentary on the significant burden of amputation to patients. Please see response to editor question #4** 2. I think the objectives and hypotheses underlying them could be more clearly specified in the abstract. I suggest authors use PICOS formulation to clarify. Please also align with those given in the manuscript. **This study represents exploratory work to understand the current context of care in Ontario. The overarching premise of our work is that integrated regional amputation prevention efforts may help save limbs for patients with diabetes and PAD. However, we appreciate the reviewer's point that this is not the hypothesis directly tested by our study. The abstract background has been changed to the following:** **"The care necessary to prevent amputation from diabetes and PAD remains disjointed in many jurisdictions. In order to help inform integrated regional amputation prevention efforts, this ecological study explores the correlation between regional health care services and rates of lower extremity amputation."** 3. Please explicitly justify the cut-off of 40 years. If it is due to the low incidence below that age – provide some data. **Please see response to editor question # 6** 4. Why only use patients who had amputations as the denominator for healthcare use rather than all patients with diabetes/PAD? **Please see response to editor question # 10** 5. I presume patients were identified with ICD-10 codes from the DAD and ICD-9 from physician billing data. Please discuss the discrepancy between the two (coding systems and data sets). **Patients were only identified using ICD-10 diagnosis and CCI codes. The full list of codes is provide in Appendix 1 Supplemental Tables 1,2,3**

	6. Inter-regional variation could be quantified with intraclass correlation coefficients **Unfortunately, a person level evaluation of the extent of variation in amputation rates is not possible for the reasons described in response to editor question #10.** 7. Rates are standardized for age and sex but there is no adjustment/stratification for comorbidities, disease severity, rurality or SES, which authors themselves identify as important risk factors (Supplemental Table 2). Can the authors conduct an adjusted analysis (difficult given low sample size but could be added as sensitivity analysis) or if not, discuss as a very important limitation. Patients who consult are more health conscious (SES, diet, exercise) and from less rural areas so the results are not really surprising. **Please see response to editor question # 10 and #14** 8. Lowest income quintile in each region is given in Supplemental table 2. Any information on social deprivation (Pampalon index)? **Lowest income quintile was available for amputees but not the general population for which amputation rates are calculated. Social and economic marginalization are now explicitly mentioned as important missing data to better understand regional amputation rates.** 9. Also mention in limitations the low sample size for correlation analysis (n=14). Some of the correlations seem very strong but are so imprecise that they are not statistically significant. Can the authors provide an idea (from the literature) of what ranges of r indicate strong, moderate and weak correlation? **As detailed in response to editor questions #11 and #12 we have now focused the analysis on the Pearson correlation coefficient. The methods also now state: "Based on effect size considerations suggested by Cohen, the magnitude of specific correlations can be interpreted according to the following criteria (where r is the absolute value of the coefficient): 0.1< r ≤0.3 denotes weak correlation; 0.3< r ≤0.5 denotes moderate correlation; r >0.5 denotes strong correlation.[22]"** 10. Please specify the time periods used for all measures. The cohort was defined 2007 to 2017. Did they retrospectively look at data from 2004 (3-years prior to amputation) for identifying cases of PAD or diabetes? How did authors deal with fluctuations in mean capita counts per region over time? How did they deal with changes from ICD9 to 10 in DAD data? **Those are the correct time periods. To ensure clarity we now specify in the methods that the 3-year look back is "relative to the index amputation". (ii) Quarterly rates were averaged over the April 1, 2007 March 31, 2017 study period. All data were in ICD-10 over the study period (dx codes from physician billing claims do exist in ICD-9 format but were not used because they are not reliable with respect to PAD. For example, a consultation to rule out PAD is coded the same as a consultation for a patient with PAD).** 11. Please justify the cut-off of 30 days for excluding visits close to amputation. With a reference would be preferable. **Physician and podiatry visits within 30 days prior to index amputation admission were not counted since visits so close to amputation are more likely to reflect the assessment and determination of a non-salvageable limb,**

	rather than an opportunity to avoid amputation. Revascularization for limb threatening ischemia is ideally performed within no longer than 4 weeks delay (https://pubmed.ncbi.nlm.nih.gov/31159978/). This is generally the case in Ontario although the Ministry Wait Time data are not publicly available. As a result, it seems reasonable to expect that any provider encounter with a meaningful opportunity to prevent major amputation would have begun at least 30 days prior to amputation. 12. Why present r and r-squared? Can simply present Pearson r if no covariables. **Thank you for this suggestion. We have modified the manuscript accordingly.** 13. Also interesting to note that mortality incidence on index visit is very high – 10% - and varies considerably across regions. **Patients with diabetes and PAD generally have ischemic heart disease and other major comorbidities. Many present late with sepsis. The mortality of 9-13% is in line expectation unfortunately.** 14. Can the authors comment on research going forward and implications for health care organisation? **Thank you. The discussion now more explicitly outlines implications and directions of future investigation.**
Reviewer 2	Dr. Sudhir Nagpal
Institution	Department of Surgery, The Ottawa Hospital, Ottawa, Ont.
General comments (author response in bold)	Does the background accurately represent current knowledge in this field? **The relatively short introduction Did not allow for an expansive review of the current literature or knowledge.** Do the authors explain why they conducted the study? **Yes** Is there a clear research question? **Yes** Is the study design appropriate? **Univariate analysis and calculating the coefficient of determination was done. (no multivariate analysis)** Are the methods described in enough detail? Did you find anything confusing? **Some of the tables are confusing see comments in review.** You may wish to consider: participants, intervention, exposure, comparator, outcome, confounders, bias Are the results reasonable? Interesting? Surprising? **Reasonable and reinforcing of the importance of arterial flow to healing** Is the interpretation supported by data in the results? **See comments in body of review.** Do tables and figures accurately represent the data? Would some other visual be

	more helpful? **See comments in body of review** Are any important limitations not mentioned? **Limitations mentioned in discussion** Did you spot any fatal flaws? That is, errors you do not believe the authors could overcome. Please explain clearly. **They may need to reevaluate the correlations of vascular surgeon numbers, or at least clarify for North east and Central west regions.** For whom are these findings relevant? **Clinicians and policymakers.** Do the authors place their findings in the context of the literature? **This was well done in the discussion as they reviewed the literature of the benefits multidisciplinary clinics and the specific importance of inline arterial flow.** **Thank you. Our responses follow the specific comments** **The purpose of this study is to evaluate the correlation between different regional health care services and lower extremity amputation related to diabetes and peripheral arterial disease. This is a provincial wide observational study divided into local health care integration networks for comparative purposes.** **The health care services variables studied (within past 1 year- physician visits (Primary, Orthopedic, Vascular, General,), publicly funded podiatry visits, emergency department visits, hospitalization, home care nursing, minor amputation, limb revascularization. Data acquired from linked databases at ICES.** Comments: 1. “Integrated regional amputation prevention efforts can help save limbs for these patients.” Pg 3 line33-34 (need reference) **“Can” corrected to “may”. This was an error is word selection and reflects an overarching premise by the authors rather than a statement based on firm evidence. This work seeks to inform such integrated regional prevention efforts.** 2. “Comorbidity index” (Aggregated Diagnosis Group Comorbidity, why was this one chosen. Appendix 2 table 2) **ADG comorbidity index includes both inpatient and outpatients encounters and has been validated as predictive of 1-year mortality in a cohort of Ontarians as referenced. This point has been added to the manuscript for clarity.** 3. Re: Table 1 Please Clarify: Intervention- Index Amputation Hospitalization- my understanding would be this was an attempt to save limb but was unsuccessful (ie index Amputation Hospitalization). How can this be negatively correlated if by definition there is 100% chance of amputation. **The correlations were evaluated at the region level rather than person level.**

	Revascularization prior to the index (amputation) hospitalization and revascularization on the index (amputation) hospitalization likely reflects attempted limb salvage at different points in a patient's clinical course. In both cases, regions with high % of revascularization had lower amputation rates. 4. Re: Supplemental Table 3: Table 3 Central West Vascular Surgeons- 0 is this correct? Is Brampton in this LHIN North East LHIN is this correct? Sudbury is in this LHIN (3 Vasc Surgeons) Would this change the results? **The reviewer has highlighted an important limitation in the provider counts we now list in the discussion of limitations. The counts for those LHINs are correct in so far as they reflect the data available to the Ministry for fiscal year 2013, when provider counts were determined (as specified in the methods). However, surgeon specialty is based on billing specialty so it is likely that vascular surgeons in these two LHINs were billing as general surgeons. The correlation coefficient for vascular surgeon per capita count with all 14 LHINS vs. when excluding those 3 LHINs remains non-significantly different from zero: - 0.44 [-0.78 ; 0.14] vs, -0.18 [-0.70; 0.47].** 5. Appendix 3 Supplemental Tables On Table 1. Rates of Major Amputation related to Diabetes. The order of LHIN's is different from Table 1 to the rest of the Tables up to 6. This puts into question the different LHINS outcomes as they were supposed to be listed in order of rates. Please clarify. **Thank you for identifying this typo in the diabetes subgroup tables. Only the LHIN name columns for Tables 2-6 were erroneous and have been corrected.** This paper shows significant differences in rates of amputation related to regional variation and density of populations. Vascular surgeons and their assessment as well as vascular interventions also appear to be correlated with reduced amputation rates. There was no difference with other physician assessments surprisingly. A significant limitation, as the authors suggest, is separating the cause of higher amputation rates from lack of access to vascular expertise; or delayed diagnosis which leads to irretrievable tissue loss. This cannot be ascertained from this study and has major implications for policy makers.