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Geographic Variation in Preventable Hospitalizations Across Canada: A Spatial Analysis

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Geographic Variation in Preventable Hospitalizations Across Canada

Abstract (261/300 words)

Objective: The objective of this study is to examine the magnitude and pattern of small-area geographic variation in rates of preventable hospitalizations for ACSC across Canada (excluding Québec).

Design and Setting: A cross-sectional study conducted in Canada (excluding Québec) using data from the 2006 Canadian Census Health and Environment Cohort (CanCHEC) linked prospectively to hospitalization records from the Discharge Abstract Database (DAD) for the three fiscal years: 2006-07, 2007-08, and 2008-09.

Primary Outcome Measure: Preventable hospitalizations (ambulatory care sensitive conditions)

Participants: The 2006 CanCHEC represents a population of 22,562,120 individuals in Canada (excluding Québec). Of this number, 2,940,150 (13.03 per cent) individuals were estimated to be hospitalized at least once during the 2006-09 fiscal years.

Methods: Age-standardized annualized ACSC hospitalization rates per 100,000 population were computed for each of the 190 Census Divisions. To assess the magnitude of Census Division-level geographic variation in rates of preventable hospitalizations, the global Moran's *I* statistic was computed. 'Hot spot' analysis was used to identify the pattern of geographic variation.

Results: The Moran's *I* statistic (Moran's $I = 0.355$) suggests non-randomness in the spatial distribution of preventable hospitalizations. The findings from the 'hot spot' analysis indicate a cluster of Census Divisions located in predominantly rural and remote parts of Ontario, Manitoba, and Saskatchewan and in eastern and northern parts of Nunavut with significantly higher than average rates of preventable hospitalization.

Conclusions: The knowledge on the magnitude and pattern of small-area geographic variation in preventable hospitalizations can inform regional, provincial, and national decision makers on planning, allocation of resources and monitoring performance of health service providers.

Geographic Variation in Preventable Hospitalizations Across Canada

Keywords

Preventable hospitalizations; ambulatory care sensitive conditions; spatial analysis

Strengths and limitations of this study

- Variation in rates of hospitalization for ambulatory care sensitive conditions is evident across larger geographic areas, including provinces and health regions in Canada.
- Our analysis indicates that there is a statistically significant level of spatial variation in preventable hospitalizations across Canada at the Census Division level.
- Census Divisions located in predominantly in rural and remote regions have higher rates of preventable hospitalizations than Census Divisions located in urban areas.
- To define geographic areas, the boundaries of Census Divisions were used and although results may differ depending on the definition of geographic units, the methodological approach adopted in this study is generalizable to other geographic units.
- Limitations of this study include the absence of hospitalization records in the Discharge Abstract Database from Québec, and the lower coverage rates for residents of the territories, young adults, individuals of lower SES, and rural residents.

Geographic Variation in Preventable Hospitalizations Across Canada

INTRODUCTION

Hospitalizations due to ambulatory care sensitive conditions (ACSC) are an important indicator of access and quality of primary care services [1-4], and therefore an important focus of health service research in Canada [1, 5, 6] and internationally [7-11]. Though not all hospitalizations are preventable, with appropriate screening, monitoring, management, and follow-up in primary care settings, many ACSC-related hospitalizations can be avoided [4, 12].

The Canadian Institute of Health Information (CIHI) compiles provincial and health region-level aggregated data on preventable hospitalizations related to the following ACSC: chronic obstructive pulmonary disease (COPD), asthma, heart failure and pulmonary edema, hypertension, angina, diabetes, and grand mal status and other epileptic convulsions [4]. The most recent, age-standardized Canadian estimates form CIHI indicate that in 2017-18, 327 per 100,000 population had an ACSC-related hospitalization, a decrease from 349 per 100,000 population in 2010 [13]. However, these national figures obscure substantial geographic variation in these rates, which has persisted since 2001 when such data became available [14]. In 2017-18, British Columbia had the lowest hospitalization rate for ACSC (294 per 100,000 population) and Nunavut had the highest rate (751 per 100,000 population), a rate approximately 2.5 times greater than in British Columbia [13]. There is also some evidence of substantial variation in these rates within provinces [6, 15-18]. Within Ontario, for example, in 2017-18, there was an almost three-fold difference in preventable hospitalization rates between the Central Local Health Integration Network (LHIN; 195 per 100,000 population) and the North-West LHIN (575 per 100,000 population, respectively) [13].

International research suggests that more pronounced differences in the rates of preventable hospitalizations may be found across smaller geographic areas (i.e., small-area variation), including administrative units responsible for the local delivery of primary care services [8, 10, 19, 20]. However, there is only limited Canadian research examining small-area variation in preventable hospitalizations. A 2008 report commissioned by the CIHI found substantial differences in age-standardized ACSC-

related hospitalization rates across 15 Census Metropolitan Areas (CMA), with Regina CMA having the highest rate of 518 per 100,000 population and Ottawa-Gatineau CMA reporting the lowest rate of 181 per 100,000 population [16]. The scope of this study, however, was restricted to a very limited number of large urban areas.

To address this gap, the objective of this study was to examine the magnitude and pattern of geographic variation in preventable hospitalizations in Canada (excluding Québec) across small geographic areas, defined by the boundaries of Census Divisions (CDs). CDs are standard census geographic units that generally correspond to municipalities, as determined by provincial and territorial legislation, or neighbouring municipalities amalgamated for the purposes of regional planning and managing some of the common services [21]. CDs vary in their areas and population sizes and, in 2006, there were 190 CDs in Canada (excluding Québec). A reference map of CDs can be found on the Statistics Canada website [22]. We hypothesized that the overall magnitude of geographic variation and the distribution of preventable hospitalizations across CDs in Canada is not random but rather exemplifies spatial dependence where CDs with lower and higher than average ACSC-related hospitalization rates are clustered together. The presence of small-area geographic differences in rates of potentially preventable hospitalizations may suggest the presence of substantial inequalities in access to appropriate primary care across CDs [6, 16, 17]. Thus, identifying CDs with disproportionately high rates of ACSC-related hospitalizations can support decision-makers in planning, allocation of resources, and monitoring performance of health service providers as well as lead to improvement in primary care quality to reduce the burden of preventable hospitalizations [23, 24]. Moreover, methodological approaches and findings from this baseline study can lend to further examination of whether or not clusters of CDs with lower or higher rates of preventable hospitalizations are emerging, stable, or declining.

METHODS

Data. To assess the magnitude and pattern of geographic variation in rates of ACSC-related hospitalization, we used the 2006 Canadian Census Health and Environment Cohort (CanCHEC) linked prospectively to hospitalization records from the 2006-2009 Discharge Abstract Database (DAD). The 2006 CanCHEC consists of about 20 per cent of the non-institutional respondents to the 2006 Census of Canada who were given long-form census questionnaire, totaling over 4.6 million individuals. The cohort reliably captures characteristics of the entire Canadian population, residing in large metropolitan regions or small remote settlements [25] as it is representative of approximately 95-97 per cent of the provincial populations and 93-94 per cent of the territorial populations [25, 26].

The individual-level records for the members of the 2006 CanCHEC were recently linked by Statistics Canada to the Discharge Abstract Database (DAD) records for three fiscal years: 2006-07, 2007-08, and 2008-09 [27]. The DAD is a census of hospital discharges for all provinces and territories excluding Québec, which does not report hospitalization data to the DAD, and includes administrative and clinical data for approximately three million hospital discharges per year [28]. The DAD provides information on the main diagnoses, date of admission, and treatment information. Each hospital record consists of up to 25 diagnoses and 20 intervention codes based on the International Classification of Disease 10th Revision, Canadian Modification codes (ICD-10-CA) and volume four of the Canadian Classification of Health Interventions [29, 30].

The record linkage of the 2006 CanCHEC and 2006-09 DAD involved the hierarchical deterministic exact method [31], and was based on personal identifiers common to both data sources (i.e., date of birth, sex, and postal code). A validation study conducted by Statistics Canada indicated that linkage rates approached 100 per cent, with weighted coverage rates exceeding 80 per cent (i.e., the weighted CanCHEC represents over 80% of hospitalizations during the 2006-09 period), and that the linked files are suitable for health-related research as the data are broadly representative of the population of all provinces and territories, excluding Québec [27]. Methodological details on the 2006 CanCHEC, data linkage, and findings from the linkage validation study are available elsewhere [27].

Rates of preventable hospitalizations. Following the CIHI's previously established definition of ACSC, validated for use in Canada [4], we used the first three characters of each 'most responsible' diagnosis to identify ACSC-related hospitalization events. Selected ACSC include grand mal status and other epileptic convulsions, COPD, asthma, diabetes, heart failure and pulmonary edema, hypertension, and angina (excluding cases with cardiac procedures). For each CD, we computed age-standardized annualized ACSC hospitalization rate per 100,000 population. Specifically, hospitalization records over three fiscal years (i.e., 2006-07, 2007-08, and 2008-09) were pooled to produce a stable estimate of ACSC-related hospitalization rate in each CD and to detect differences between these geographic areas. Sampling weights were used in line with the 2006 census design. The estimated population-level counts of hospitalization events in each CD were rounded to a base of 5 as required by Statistic Canada's confidentiality procedures. The rate for each CD was computed by dividing the estimated annualized and rounded count of ACSC-related hospitalizations in that CD by the total population of that CD and then expressed as per 100,000 population. Finally, direct standardization was carried out using the entire 2006 Census Canada as the reference population and four age groups (i.e., 0-19 years, 20-39, 40-59, 60 and over).

Statistical analysis. To assess the magnitude of CD-level variation (i.e., spatial autocorrelation) in rates of preventable hospitalizations, we computed the global Moran's *I* statistic which assesses the degree to which rates are similar or dissimilar across geographic areas [32]. This was computed using the formula:

$$I = \left(\frac{n}{S_0}\right)\frac{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij} z_i z_j}{\sum_{i=1}^{n} z_i^2}$$

where, z_i and z_j for areas i and j are the deviations from the mean, w_{ij} is the matrix of row-standardized weights, and

$$S_0 = \sum_{i=1}^{n} \sum_{j=1}^{n} w_{ij}$$

Moran's *I* values range from -1 to +1, which represent extreme negative and positive spatial correlations, respectively (i.e. CDs with either low or high preventable hospitalization rates are geographically clustered together) and 0 indicating spatial randomness (no spatial correlation across CDs). To test the null hypothesis of no spatial correlation, a Monte Carlo simulation was used with 1,000 random permutations to produce the rank of observed Moran's *I* in relation to the simulated values, with $p < 0.05$ indicating statistical significance.

To determine the location of clusters of CDs with significantly lower (i.e., 'cold spots') or higher (i.e., 'hot spots') ACSC hospitalization rates, we assessed whether preventable hospitalization rate in each CD is closer to the rates of its neighbours or to the national average. This was achieved using the local indicator of spatial association (LISA) [32, 33] using the formula:

$$I_i = z_i \sum_{j=1}^{n} w_{ij} z_j$$

The statistical significance of LISA estimates was tested using a Monte Carlo simulation which compares the actual observed LISA values for each CD with the distribution of repeatedly randomized values. A LISA significance map was produced to identify clusters of CDs with significantly higher or lower rates of ACSC hospitalizations compared to their neighbors. All analyses were conducted using R [34].

RESULTS

The 2006 CanCHEC represents a population of 22,562,120 individuals in Canada, except Québec. Of this number, 2,940,150 (13.03 per cent) individuals were estimated to be hospitalized at least once during the 2006-09 fiscal years. In total, the weighted number of hospitalization events reported by all members of this population was 4,762,195. Out of that number, 337,995 (7.10 per cent)

events were ACSC-related hospitalizations. The most common ACSC diagnosis was COPD, followed by heart failure and pulmonary edema, angina, diabetes, asthma, grand mal, and hypertension.

The overall annualized rate of preventable hospitalization for the 2006 CanCHEC for the 2006-09 fiscal years was 499 per 100,000 population (see Table 1). The rates of ACSC-related hospitalizations varied across provinces and territories from the lowest of 436 per 100,000 population in British Columbia to the highest of 1,264 per 100,000 population in Nunavut. As hypothesized, the across CD variation in these rates was even more pronounced than the variation across provinces, with the rates ranging from the lowest of 266 per 100,000 population in the White Horse Plains area near the city of Winnipeg in Manitoba to the highest of 2,131 per 100,000 population in Manitoulin, in central Ontario. The median rate across all CDs was 693 per 100,000 population with the inter-quartile range equal to 351 (i.e., from 564 and 915 per 100,000 population). Similarly, a substantial level of variation can also be observed across CDs within each province. Figure 1 displays the rates of preventable hospitalizations for all CDs in Canada (excluding Québec) and suggests that there is a substantial level of variation in these rates across Canada and within each province and territory. In general, the rates appear to be highest in CDs located in the northern parts of Newfoundland and Labrador, New Brunswick, Ontario, Manitoba, Saskatchewan, and Alberta. They are also relatively high in the interior of British Columbia and in some parts of Nunavut and the Northwest Territories.

Geographic Variation in Preventable Hospitalizations Across Canada

Table 1. Ambulatory Care Sensitive Condition Hospitalization Rates across Provinces and Census Divisions, Canada 2006-2009

					ACSC rates across CDs within each province		
Province	**Population** (1)	**ACSC Events** (2)	**ACSC Rates** (3)	**# CDs**	**Lowest**	**Median**	**Highest**
Newfoundland and Labrador	474,405	9,265	651	11	513	513	1,054
Prince Edward Island	125,800	2,720	721	3	672	779	780
Nova Scotia	853,525	13,335	521	18	368	643	1,353
New Brunswick	696,650	17,465	836	15	566	846	1,094
Ontario	11,428,170	154,715	451	49	296	581	2,131
Manitoba	1,082,900	19,595	603	23	266	827	2,112
Saskatchewan	907,630	23,375	858	18	518	1,063	1,576
Alberta	3,088,730	45,325	489	19	373	708	1,401
British Columbia	3,810,320	49,850	436	28	331	616	1,244
Yukon	28,770	460	533	1	533	533	533
Northwest Territories	38,440	875	759	2	667	876	1,085
Nunavut	26,775	1,015	1,264	3	564	1,215	1,540
Canada	22,562,120	337,995	499	190	266	693	2,131

ACSC, Ambulatory Care Sensitive Condition; CD, Census Division

(1) 2006 population size rounded to a base of 10

(2) Estimated population-level counts of ACSC hospitalization events rounded to a base of 5

(3) Standardized and annualized ACSC hospitalization rates per 100,000 population

Geographic Variation in Preventable Hospitalizations Across Canada

[Insert Figure 1]

The Moran's *I* statistic, computed to assess the overall magnitude of variation in preventable hospitalization rates across CDs, was 0.3550 (expected value = -0.0053; variance = 0.0026) suggesting that the overall spatial distribution of preventable hospitalizations across CDs is non-random. The results from the Monte-Carlo simulation of Moran's *I* indicated that the null hypothesis of no spatial correlation can be rejected (the rank of the observed Moran's *I* = 1,000; the pseudo *p*-value = 0.001).

Figure 2 presents the findings from the LISA analysis and depicts the pattern of clustering of CDs with significantly higher ('hot spots') and lower ('cold spots') rates of preventable hospitalizations. It indicates that a relatively large cluster of CDs with higher than average hospitalization rates was located in northern parts of Ontario, Manitoba, and Saskatchewan and across eastern and northern parts of Nunavut ('hot spots'). In addition, two clusters of CDs with lower than average rates ('cold spots') were found, one in the Greater Toronto Area, and one in central Nova Scotia, around the town of Windsor.

[Insert Figure 2]

DISCUSSION

This study addresses an important gap in the literature by providing information on the magnitude and pattern of geographic variation in preventable hospitalizations in Canada. Specifically, our study contributes to the literature by: (1) providing a quantitative assessment of the magnitude of spatial variation in preventable hospitalizations across small geographic areas (i.e., CDs); (2) identifying geographic areas with significantly lower or higher concentrations of these events (i.e., 'cold spots' and 'hot spots', respectively); and (3) demonstrating how spatial analysis can be applied to future studies of geographic variation in preventable hospitalizations that may involve data on newer census cohorts linked to more recent hospitalization records, when these data become available.

Overall, the results of the spatial analysis provide support for the hypothesis that there is a statistically significant and substantial level of spatial variation in preventable hospitalizations across

Canada and clustering of CDs with significantly lower and higher rates, which is a novel finding as the previous studies did not conduct any formal statistical assessment of the magnitude or patterns of geographic variations. The presence of a large cluster of CDs with higher than average ACSC-related hospitalization rates, stretching from northern parts of Ontario, Manitoba, and Saskatchewan and across eastern and northern parts of Nunavut, indicates that CDs with significantly higher rates of preventable hospitalizations are more likely to cluster in northern, predominantly rural and remote regions of Canada. In a CIHI report, rural areas in Canada were found to have approximately 60 per cent higher rates of preventable hospitalizations compared to urban areas [14], potentially due to poor access to primary care in these locations [35, 36]. In contrast, two 'cold spots', characterized by lower than average rates of preventable hospitalizations, were found in predominately urban areas (i.e., in the Greater Toronto Area and in the urban area of Nova Scotia). This pattern is likely related to differential levels of primary care supply in rural and urban areas as characteristics of the health care system that stem from barriers related to access to and quality of primary care services is one of the major driver of geographic variation in preventable hospitalizations [7, 23, 24].

It is important to acknowledge that, in addition to availability of health care services, the magnitude and pattern of geographic variation in preventable hospitalizations may also be related to differences in socio-demographics, health behaviors, and/or health status characteristics of the individuals residing in each CD (i.e., compositional effect) or to other area-level factors. Berlin et al. [8] argue that although an effective primary care system should aid in the prevention of ACSC-related hospitalizations, these events are also dependent on individual-level factors such as propensity to seek care, severity of disease, compliance issues, financial constraints, or accessibility issues. Research by Falster and colleagues [20] suggests that as much as 36.9 per cent of geographic variation in preventable hospitalizations in Australia was a result of individual-level sociodemographic and health characteristics. The geographic variation in preventable hospitalizations may, in particular, be driven by the well-known social gradient in health, as described by Marmot and colleagues [37]. In a 2008

study involving 15 CMA areas, for instance, hospitalizations for ACSC were highest among those with low socio-economic status (SES) and showed a steep gradient between low SES, average SES, and high SES [16]. Thus, further examination of the determinants of geographic variation, with a focus on individual-level factors, would help ascertain why residents of some CDs are more (or less) likely to be hospitalized for an ACSC, compared to residents in other areas of Canada.

Limitations. One limitation of any analysis involving the DAD is the absence of hospitalization records from Québec. Since these records are currently not shared with the CIHI or Statistics Canada, we were not able to directly address this limitation. Second, the validation study of the 2006 CanCHEC-DAD linked files indicated that coverage rates were slightly lower for residents of the territories, young adults, individuals of lower SES, and rural residents [27]; however, sampling weights used to extrapolate the observed counts to the whole population accounted for some of this underrepresentation. Furthermore, the boundaries of CDs were used in this study to define geographic areas. Although the Modifiable Areal Unit Problem indicates that the results may differ depending on the definition of geographic units [38-40], the methodological approach adopted in this study is generalizable to other geographic units. The results of this study are also based on the assumption that during the 2006-09 time period, members of the 2006 CanCHEC did not move from CDs that they reported as their home addresses in the 2006 Census; however, residential mobility within the boundaries of each CD would not affect the results. Lastly, estimates generated from the recently released 2006 CanCHEC-DAD linked files may not reflect the current rates of preventable hospitalization in Canada. However, at present, these are the best national data that are available for conducting analysis on small-area geographic variation in preventable hospitalizations. Moreover, for surveillance purposes, findings from the current study can be used as a baseline estimate to be compared with the results of future assessments of geographic variation in preventable hospitalization involving linked files from newer census cohorts, when these data become available.

CONCLUSIONS

Geographic Variation in Preventable Hospitalizations Across Canada

The knowledge on the magnitude and pattern of small-area geographic variation in preventable hospitalizations can inform regional, provincial, and national decision makers on planning resources and monitoring performance of health service providers. Since preventable hospitalizations are an important indicator of access and quality of primary care services, identifying of clusters of CDs with disproportionately high rates of ACSC-related hospitalizations can lead to improvement in primary care quality in these areas to reduce the burden of preventable hospitalizations. Ultimately, this can lead to the reduction of substantial inequalities in the rates of preventable hospitalizations across Canada.

The current study provides valuable insight into small-area geographic variation in preventable hospitalizations in Canada. We found that the pattern of 'hot spots' in ACSC-related hospitalizations do not follow provincial boundaries, which is a novel observation in the Canadian context and suggests the need to focus on intra-provincial comparisons. As suggested by the existing literature, there may be a wide range of interrelated factors that can potentially contribute to this variation. Although it is often assumed that small-area geographic variation in preventable hospitalizations is related to characteristics of the health care system, this variation may also be related to individual- and area-level socioeconomic factors rooted in the local contexts [10, 20, 23]. Ultimately, people interact with the health care system in the geographic areas in which they reside, and future research should assess the nature of these interactions and how they may contribute to the observed geographic variation in ACSC-related hospitalizations.

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Contributors

All authors contributed to the design of the study. PW planned and undertook statistical analysis and interpretation. PW and AM drafted and finalized the manuscript with review by SA, KA, AC, MC, SF, JG, MH, SH, SK, KN, RP, S Sarma, S Singh, S Stranges, and AT. All authors reviewed, commented on and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PW had full access to the data.

Ethics

Ethical approval for this study was not required as the study uses anonymous and confidential secondary data from Statistics Canada. Consent from respondents was obtained at the time of data collection. Data were provided by Statistics Canada through the Research Data Centres program and accessed under the *Statistics Act* of Canada. The analyses and the interpretation are the authors' alone.

Patient and Public Involvement

Patients were not involved in this study.

Data availability statement

No data are available.

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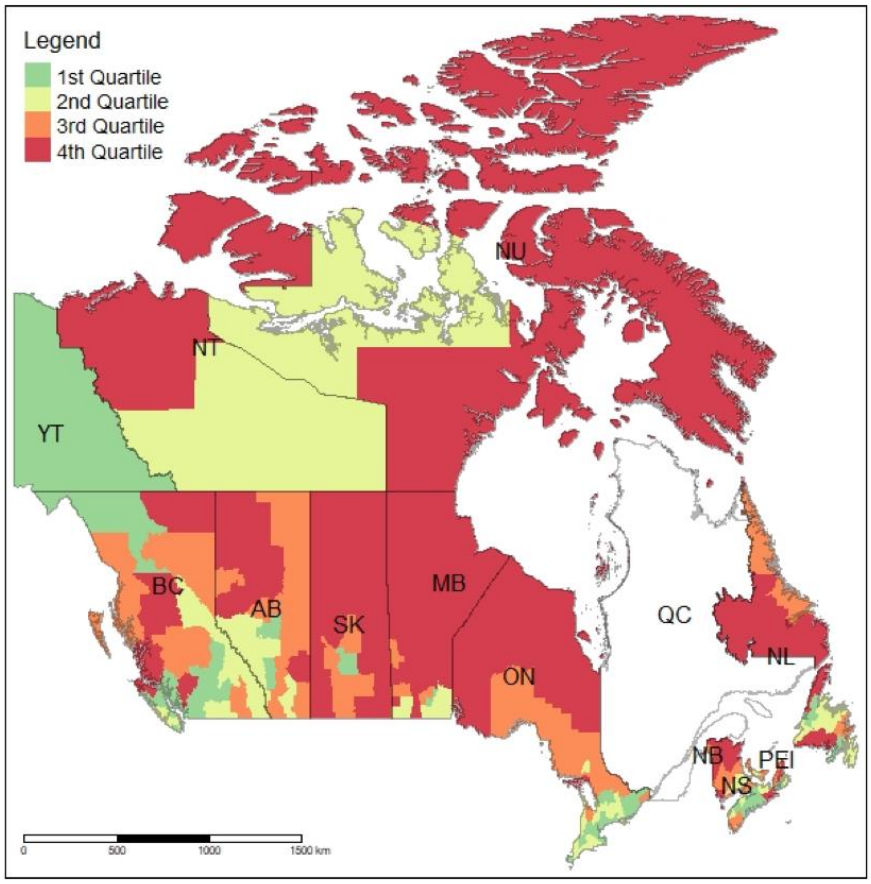

Figure 1. Age-Standardized Annualized Hospitalization Rates (quartiles) for Ambulatory Care Sensitive Conditions per 100,000 population: Canada (Census Divisions)

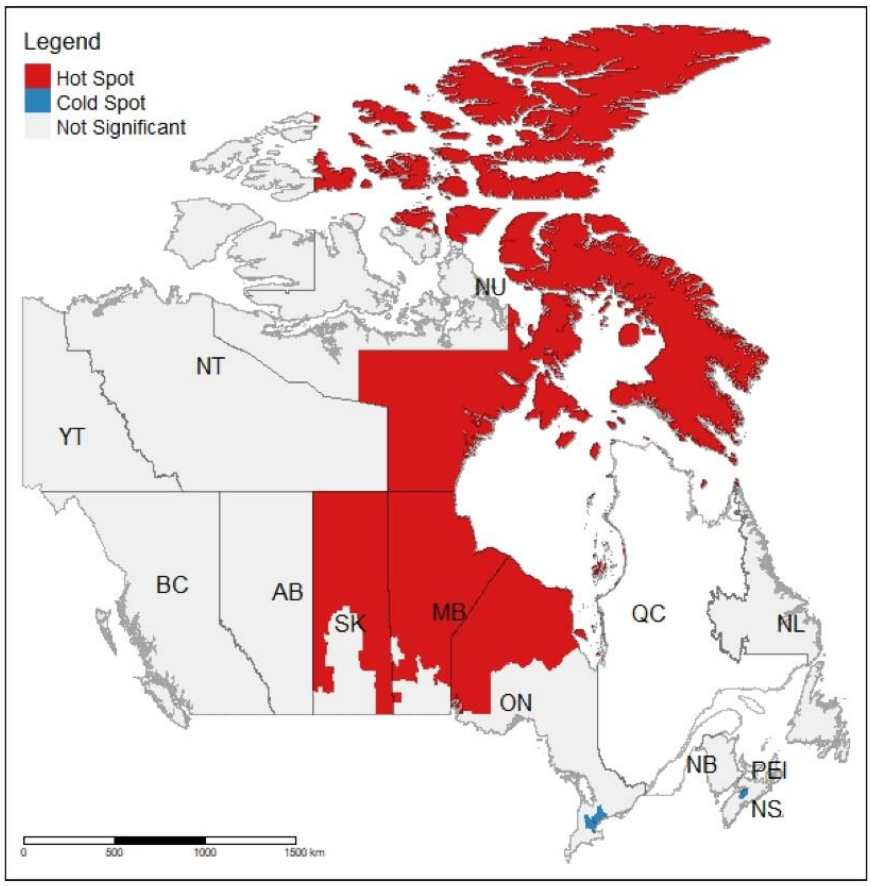

Figure 2. Hot Spots and Cold Spots in Preventable Hospitalizations: Canada (Census Divisions)

Note: This map identifies clusters of Census Divisions with significantly higher (hots spots) or lower (cold spots) rates of hospitalizations for ambulatory care sensitive conditions compared to their neighbors.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Geographic Variationin Preventable Hospitalizations AcrossCanada: A Cross-sectional Study

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Geographic Variation in Preventable Hospitalizations Across Canada

Abstract (281/300 words)

Objective: The objective of this study is to examine the magnitude and pattern of small-area geographicvariation in rates of preventable hospitalizations for ambulatory care sensitive conditions (ACSC) across Canada (excluding Québec).

Design and Setting: A cross-sectional study conducted in Canada (excluding Québec) using data from the 2006 Canadian Census Health and Environment Cohort (CanCHEC) linked prospectively to hospitalization records from the Discharge Abstract Database (DAD) for the three fiscal years: 2006-07, 2007-08, and 2008-09.

Primary Outcome Measure: Preventable hospitalizations (ACSC)

Participants: The 2006 CanCHECrepresents a population of 22,562,120individuals in Canada (excludingQuébec). Of this number, 2,940,150 (13.03 per cent) individuals were estimated to be hospitalized at least once during the 2006-09 fiscal years.

Methods:Age-standardized annualized ACSC hospitalization rates per 100,000 populationwere computed for each of the 190 Census Divisions.To assess the magnitude of Census Division-levelgeographic variation in rates of preventable hospitalizations, the global Moran's *I* statistic was computed. 'Hot spot' analysis was used to identify the pattern of geographic variation.

Results:Of all the hospitalization events reported in Canada during the 2006-09 fiscal years, 337,995 (7.10 per cent) events were ACSC-related hospitalizations. The Moran's *I* statistic (Moran's I = 0.355)suggests non-randomness in the spatial distribution of preventable hospitalizations. The findings from the 'hot spot' analysis indicatea cluster of Census Divisionslocated in predominantly rural and remote parts of Ontario, Manitoba, and Saskatchewan and in eastern and northern parts of Nunavut with significantly higher than average rates of preventable hospitalization.

Conclusions:The knowledge generated on the small-area geographic variation in preventable hospitalizations can inform regional, provincial, and national decision makerson planning,allocation ofresources and monitoring performance of health service providers.

Keywords

Preventable hospitalizations; ambulatory care sensitive conditions; spatial analysis

Strengths and limitations of this study

- This study examines the geographic variation in rates of ACSC-related hospitalization using the 2006 Canadian Census Health and Environment Cohort (CanCHEC) linked prospectively to hospitalization records from the 2006-2009 Discharge Abstract Database (DAD).
- Wedetermined the magnitude of Census Division-level variation (i.e., spatial autocorrelation) in rates of ACSC-related hospitalizations by computing the global Moran's *I* statistic, which assesses the degree to which rates are similar or dissimilar across geographic areas.
- We identified the location of clusters of Census Divisions with significantly lower (i.e., 'cold spots') or higher (i.e., 'hot spots') ACSC hospitalization rates using the local indicator of spatial association (LISA).
- Geographic areas were defined using the boundaries of Census Divisions,and although results may differ depending on the definition of geographic units, the methodological approach adopted in this study is generalizable to other geographic units.
- Limitations of this study include the absence of hospitalization records in the Discharge Abstract Database from Québec, and the lower coverage rates for residents of the territories, young adults, individuals of lower socio-economic status, and rural residents.

INTRODUCTION

Hospitalizations due to ambulatory care sensitive conditions (ACSC)are an important indicator of access and quality of primary care services[1-4],and therefore an important focusof health service research in Canada[1, 5, 6] and internationally[7-11].Though not all hospitalizations are preventable, with appropriate screening, monitoring, management, and follow-up inprimary care settings, many ACSC-related hospitalizations can be avoided[4, 12].

The Canadian Institute of Health Information (CIHI)compiles provincial and health region-level aggregated data onpreventable hospitalizations related to the following ACSC: chronic obstructive pulmonary disease (COPD), asthma, heart failure and pulmonary edema, hypertension, angina, diabetes, and grand mal status and other epileptic convulsions[4].The most recent, age-standardized Canadianestimates form CIHI indicate that in 2017-18, 327 per 100,000population had an ACSC-related hospitalization, a decreasefrom 349 per 100,000 populationin 2010[13].However, these national figures obscure substantial geographic variation in these rates, which has persisted since 2001 when such data became available[14]. In 2017-18, British Columbia had the lowest hospitalization rate for ACSC (294 per 100,000population) and Nunavut had the highest rate (751 per 100,000population), a rate approximately 2.5times greaterthan in British Columbia[13].There is also some evidence of substantial variation in these rates within provinces[6, 15-18].Within Ontario, for example, in 2017-18,there was an almost three-fold difference in preventable hospitalization rates between the CentralLocal Health Integration Network(LHIN; 195 per 100,000population) and the North-West LHIN (575 per 100,000population, respectively)[13].

International research suggests that more pronounced differences in the rates of preventable hospitalizations maybe found across smaller geographic areas(i.e., small-area variation), includingadministrative units responsible for the local delivery of primary care services[8, 10, 19, 20].However, there is only limited Canadian research examining small-area variation in preventable hospitalizations.A2008 report commissioned bythe CIHI found substantial differences in age-

standardized ACSC-related hospitalization rates across 15 Census Metropolitan Areas (CMA), with Regina CMA having the highest rate of 518 per 100,000 populationand Ottawa-GatineauCMA reporting the lowest rate of 181 per 100,000 population[16].The scope of this study, however, was restricted to a very limited number of large urban areas.

To address this gap, the objective of this study was to examinethe magnitude and pattern of geographic variationin preventable hospitalizationsin Canada (excluding Québec)across small geographic areas, defined by the boundaries of Census Divisions (CDs).CDs are standard census geographic units that generally correspond to municipalities, as determined by provincial and territorial legislation, or neighbouring municipalities amalgamated for the purposes of regional planning and managing some of the common services[21]. CDs vary in their areas and population sizes and, in 2006, there were 190 CDs in Canada (excluding Québec). A reference map of CDs can be found on the Statistics Canada website[22].We hypothesized that the overall magnitude of geographic variation and the distributionof preventable hospitalizations across CDs in Canada is not random but rather exemplifies spatial dependence where CDswith lower and higher than average ACSC-related hospitalization rates are clustered together. The presence of small-area geographic differences in rates of potentially preventable hospitalizations may suggest the presence of substantial inequalities in access to appropriate primary care across CDs[6, 16, 17]. Thus, identifying CDs with disproportionately high rates of ACSC-related hospitalizations can support decision-makers in planning,allocation of resources,and monitoring performance of health service providers as well as lead to improvement in primary care quality to reduce the burden of preventable hospitalizations[23, 24]. Moreover, methodological approaches and findings from this baseline study can lend to further examination of whether or not clusters of CDs with lower or higher rates of preventable hospitalizations are emerging, stable, or declining.

METHODS

Data. To assess the magnitude and pattern of geographic variation in rates of ACSC-related hospitalization, we conducted a cross-sectional study using the 2006 Canadian Census Health and Environment Cohort (CanCHEC) linked prospectively to hospitalization records from the 2006-2009 Discharge Abstract Database (DAD). The 2006 CanCHECconsists of about 20 per cent of the non-institutional respondents to the 2006 Census of Canada who were given long-form census questionnaire,totaling over 4.6 million individuals. The cohort reliably captures characteristics of the entire Canadian population, residing in large metropolitan regions or small remote settlements[25] as it is representative of approximately 95-97 per cent of the provincial populations and 93-94 per cent of the territorial populations[25, 26].

The individual-level records for the members of the 2006 CanCHEC were recently linked by Statistics Canada to the Discharge Abstract Database (DAD) records for three fiscal years: 2006-07, 2007-08, and 2008-09[27].The DAD is a census of hospital discharges for all provinces and territoriesexcluding Québec, which does not report hospitalization data to the DAD, and includes administrative and clinical data for approximately three million hospital discharges per year[28]. The DAD provides information on the main diagnoses, date of admission, and treatment information. Each hospital record consists of up to 25 diagnoses and 20 intervention codes based on the International Classification of Disease 10th Revision, Canadian Modification codes (ICD-10-CA) and volume four of the Canadian Classification of Health Interventions[29, 30].

The record linkage of the 2006 CanCHEC and 2006-09 DAD involved the hierarchical deterministic exact method[31], and was based on personal identifiers common to both data sources(i.e., date of birth, sex, and postal code). A validation study conducted by Statistics Canada indicatedthat linkage rates approached 100 per cent,with weighted coverage rates exceeding 80 per cent(i.e., the weighted CanCHECrepresents over 80% of hospitalizations during the 2006-09 period), and that the linked filesaresuitable for health-related research as the data are broadly representative of the population of all provinces and territories, excluding Québec[27]. Methodological details on the

2006 CanCHEC, data linkage, and findings from the linkage validation study are available elsewhere[27].

Rates of preventable hospitalizations. Following the CIHI's previously establisheddefinition of ACSC, validated for use in Canada[4],we used the first three characters of each 'most responsible' diagnosis to identify ACSC-related hospitalization events. Selected ACSC include grand mal status and other epileptic convulsions, COPD, asthma, diabetes, heart failure and pulmonary edema, hypertension, and angina (excluding cases with cardiac procedures).For each CD, we computed age-standardizedannualizedACSC hospitalization rateper 100,000 population. Specifically, hospitalization records over three fiscal years (i.e., 2006-07, 2007-08, and 2008-09) were pooled to produce a stable estimate of ACSC-related hospitalization rate in each CD and to detect differences between these geographic areas.Sampling weights were used in line with the 2006 census design.The estimated population-level counts of hospitalization events in each CD were rounded to a base of 5 as required by Statistic Canada's confidentiality procedures. The rate for each CD was computedby dividing the estimated annualized and rounded count of ACSC-related hospitalizations in that CD by the total population of that CD and then expressed as per 100,000 population. Finally, direct standardization was carried out using the entire 2006 Census Canada as the reference population and four age groups (i.e., 0-19 years, 20-39, 40-59, 60 and over).

Patient and Public Involvement. No patients involved.

Statistical analysis. To assess the magnitude of CD-levelvariation (i.e., spatial autocorrelation) in rates of preventablehospitalizations, we computed the global Moran's *I* statistic which assesses the degree to which rates are similar or dissimilar across geographic areas[32].This was computed using the formula:

$$I = \left(\frac{n}{S_0}\right)\frac{\sum_{i=1}^{n}\sum_{j=1}^{n} w_{ij} z_i z_j}{\sum_{i=1}^{n} z_i^2}$$

where, $z_i$and z_j for areas*i* and *j* are the deviations from the mean,w_{ij} is the matrix of row-standardized weights, and

$$S_0 = \sum_{i=1}^{n} \sum_{j=1}^{n} w_{ij}$$

Moran's *I* values range from -1 to +1, which represent extremenegative and positive spatial correlations, respectively (i.e. CDswith either low or high preventable hospitalization rates are geographically clustered together) and 0 indicating spatial randomness (no spatial correlation betweenCDs).To test the null hypothesis of no spatial correlation, a Monte Carlo simulation was used with 1,000 random permutations to produce the rank of observed Moran's *I* in relation to the simulated values, with $p < 0.05$ indicating statistical significance.

To determine the location of clusters of CDs with significantly lower(i.e., 'cold spots') or higher(i.e., 'hot spots')ACSC hospitalization rates,we assessed whether preventable hospitalization rate in each CD is closer to the ratesof its neighbours or to the national average. This was achieved using the local indicator of spatial association (LISA)[32, 33]using the formula:

$$I_i = z_i \sum_{j=1}^{n} w_{ij} z_j$$

The statistical significance of LISA estimateswastested using a Monte Carlo simulation which comparesthe actual observed LISA values for each CD with the distribution of repeatedly randomized values.A LISA significance map was produced to identify clusters of CDs with significantly higher or lower rates of ACSC hospitalizations compared to their neighbors. All analyses were conducted using R[34].Patients were not involved in this study.

RESULTS

The 2006 CanCHECrepresents a population of 22,562,120individuals in Canada, except Québec. Ofthis number, 2,940,150 (13.03 per cent)individuals were estimated to be hospitalized at least once during the 2006-09 fiscal years.In total, the weighted number of hospitalization events reported by

all members of this populationwas 4,762,195. Out of that number, 337,995(7.10 per cent) events were ACSC-related hospitalizations.The most common ACSC diagnosis was COPD (33.23%),followed by heart failure and pulmonary edema (26.10%),angina (16.01%), diabetes (9.47%), asthma (7.15%), grand mal (5.05%), and hypertension (2.99%).

The overall annualized rate of preventable hospitalization for the 2006 CanCHECforthe 2006-09 fiscal yearswas 499per 100,000 population (see Table 1).The rates of ACSC-related hospitalizations varied across provinces and territories from the lowest of 436per 100,000 populationin British Columbia to the highest of 1,264per 100,000 population in Nunavut.As hypothesized, the between CD variation in these rates was even more pronounced than the variation across provinces,with the rates ranging from the lowestof 266per 100,000 population in the White Horse Plains area near the city of Winnipeg in Manitobato the highest of 2,131 per 100,000 population in Manitoulin, in central Ontario.The median rate across all CDs was 693 per 100,000 population with the inter-quartile range equal to 351 (i.e., from 564 and 915 per 100,000 population).Similarly,a substantial level of variation can also be observed between CDs within each province. Figure 1 displays the rates of preventable hospitalizations for all CDs in Canada (excluding Québec) and suggests that there is a substantial level of variation in these ratesacross Canada and within each province and territory. In general,the rates appear to be highest in CDs located in the northernparts of Newfoundland and Labrador, New Brunswick, Ontario, Manitoba, Saskatchewan, and Alberta. Theyare also relatively high in the interior of British Columbia and in some parts of Nunavut and the Northwest Territories.

Table 1. Ambulatory Care Sensitive Condition Hospitalization Rates across Provinces and Census Divisions, Canada 2006-2009

					ACSC rates betweenCDs within each province		
Province	**Population** (1)	**ACSC Events** (2)	**ACSC Rates** (3)	**#CDs**	**Lowest**	**Median**	**Highest**
Newfoundland and Labrador	474,405	9,265	651	11	513	513	1,054
Prince Edward Island	125,800	2,720	721	3	672	779	780
Nova Scotia	853,525	13,335	521	18	368	643	1,353
New Brunswick	696,650	17,465	836	15	566	846	1,094
Ontario	11,428,170	154,715	451	49	296	581	2,131
Manitoba	1,082,900	19,595	603	23	266	827	2,112
Saskatchewan	907,630	23,375	858	18	518	1,063	1,576
Alberta	3,088,730	45,325	489	19	373	708	1,401
British Columbia	3,810,320	49,850	436	28	331	616	1,244
Yukon	28,770	460	533	1	533	533	533
Northwest Territories	38,440	875	759	2	667	876	1,085
Nunavut	26,775	1,015	1,264	3	564	1,215	1,540
Canada	22,562,120	337,995	499	190	266	693	2,131

ACSC, Ambulatory Care Sensitive Condition; CD, Census Division

(1) 2006 population size rounded to a base of 10

(2) Estimated population-level counts of ACSC hospitalization events rounded to a base of 5

(3) Standardized and annualized ACSC hospitalization rates per 100,000 population

Geographic Variation in Preventable Hospitalizations Across Canada

[InsertFigure 1]

The Moran's *I* statistic, computed to assess the overall magnitude of variationin preventable hospitalization rates betweenCDs,was 0.3550 (expected value = -0.0053; variance = 0.0026)suggesting that the overall spatial distribution of preventable hospitalizations between CDs is non-random. The results from the Monte-Carlo simulation of Moran's *I* indicated that the null hypothesis of no spatial correlation can be rejected (the rank of the observed Moran's *I* = 1,000; the pseudo *p*-value = 0.001).

Figure 2presents the findings from the LISA analysis and depicts the pattern of clustering of CDs with significantly higher ('hot spots') and lower ('cold spots') rates of preventable hospitalizations. It indicates that a relatively large cluster of CDs with higher than average hospitalization rateswas located in northern parts of Ontario, Manitoba, and Saskatchewan and across eastern and northern parts of Nunavut ('hot spots'). In addition, twoclusters of CDs with lower than average rates ('cold spots') were found, one in the Greater Toronto Area, and one in central Nova Scotia, around the town of Windsor.

[Insert Figure 2]

DISCUSSION

This study addresses an important gap in the literature by providing information on the magnitude and pattern of geographic variation in preventable hospitalizations in Canada.Specifically, our study contributes to the literature by:(1) providing a quantitative assessment of the magnitude of spatial variation in preventable hospitalizations across small geographic areas (i.e., CDs); (2) identifying geographic areas with significantly lower or higher concentrations of these events(i.e., 'cold spots' and 'hot spots', respectively); and (3) demonstrating how spatial analysis can be applied to future studies of geographic variation in preventable hospitalizations that may involve data on newer census cohorts linked to more recent hospitalization records, whenthese databecome available.

Overall, the results of the spatial analysis provide support for the hypothesis that there is a statistically significant and substantial level of spatial variation in preventable hospitalizations across

Canadaand clustering of CDs with significantly lower and higher rates, which is a novel finding as the previous studies did not conduct any formal statistical assessment of the magnitude or patterns of geographic variations. The presence of a large cluster of CDswith higher than averageACSC-related hospitalization rates,stretching from northern parts of Ontario, Manitoba, and Saskatchewan and across eastern and northern parts of Nunavut,indicates that CDswith significantly higher rates of preventable hospitalizations are more likely to cluster in northern, predominantly rural and remote regions of Canada.In a CIHI report, ruralareas in Canada were found to have approximately 60 per cent higher rates of preventablehospitalizations compared to urban areas[14], potentially due to poor access to primary care in these locations[35, 36].In contrast, two'cold spots', characterized by lower than average rates of preventable hospitalizations, were found in predominately urbanareas (i.e., in the Greater Toronto Area and in the urban area of Nova Scotia).This pattern is likely related to differences in primary health care in rural compared to urban areas, as barriers related to accessibility (e.g., availability) or quality of primary care services are well known factors related to geographic variation in preventable hospitalizations[7, 23, 24].

It is important to acknowledge that, in addition to availability of primary health care services,the magnitude and pattern of geographic variation in preventable hospitalizations may also be related to differences in socio-demographics, health behaviors, and/or health status characteristics of the individuals residing in eachCD (i.e., compositional effect) or to otherarea-level factors.Berlin et al.[8] argue that although an effective primary care system should aid in the prevention of ACSC-related hospitalizations, these events are also dependent on individual-level factors such as propensity to seek care, severity of disease, compliance issues, financial constraints, or accessibility issues. Research by Falster and colleagues[20]suggeststhat as much as 36.9 per cent of geographic variation in preventable hospitalizations in Australia was a result of individual-level sociodemographic and health characteristics.The geographic variation in preventable hospitalizations may, in particular, be driven by the well-known social gradient in health, as described by Marmot and colleagues[37]. In a 2008

studyinvolving 15 CMA areas, for instance, hospitalizations for ACSC were highest among those with low socio-economic status (SES) and showed a steep gradient between low SES, average SES, and high SES[16]. Thus, further examination of the determinants of geographic variation,with a focus on individual-level factors,would help ascertain why residents of someCDsare more (or less) likely to be hospitalized for an ACSC, compared to residents inother areas of Canada.

Limitations.One limitation of any analysis involving the DAD is the absence of hospitalization records from Québec. Since these records are currently not shared with the CIHI or Statistics Canada, we were not able to directly address this limitation. Second, the validation study of the 2006 CanCHEC-DAD linked filesindicatedthat coverage rates were slightly lower for residents of the territories, young adults, individuals of lower SES, and rural residents[27];however, sampling weights used to extrapolate the observed counts to the whole populationaccounted for some of this underrepresentation. Furthermore,the boundaries of CDs were used in this study to define geographic areas. Althoughthe Modifiable Areal Unit Problem indicates that the results may differ depending on the definition of geographic units[38-40],the methodological approach adopted in this study is generalizable to other geographic units. The results of this study are also based on the assumption that during the 2006-09 time period,members of the 2006 CanCHECdid not move from CDs that they reported as their home addresses in the 2006 Census; however, residential mobility within the boundaries of each CD would not affect the results.Lastly, estimates generated from the recently released 2006 CanCHEC-DAD linked files may not reflect the current rates of preventable hospitalization in Canada.

Additionally, the CIHI definition of ACSC may not capture all preventable hospitalizations and not all ACSC hospitalizations may be preventable [4, 12]. However, at present, these are the best national data that are available for conducting analysis on small-area geographic variation in preventable hospitalizations.Moreover, for surveillance purposes, findings from the current study can be used as a baseline estimate to be compared with the results of future assessments of geographic

variation in preventable hospitalization involving linked files from newer census cohorts, when these data become available.

CONCLUSIONS

The knowledge on the magnitude and pattern of small-area geographic variation in preventable hospitalizations can inform regional, provincial, and national decision makersonplanning resources and monitoring performance of health service providers. Since preventable hospitalizations are an important indicator of access and quality of primary care services,identifying of clusters of CDs with disproportionately high rates of ACSC-related hospitalizations can lead to improvement in primary care quality in these areas to reduce the burden of preventable hospitalizations. Ultimately, this can lead to the reduction of substantial inequalities in the rates of preventable hospitalizations across Canada.

The current study provides valuable insight into small-area geographic variation in preventable hospitalizations in Canada. We found that the pattern of 'hot spots'in ACSC-related hospitalizations do notfollow provincial boundaries, which is a novel observation in the Canadian context and suggests the need to focus on intra-provincial comparisons. As suggested by the existing literature, there may be a wide range of interrelated factors that can potentially contribute to this variation.Although it is often assumed that small-area geographic variation in preventable hospitalizations is related to characteristics of thehealth care system, this variation may also be related to individual- and area-level socioeconomic factors rooted in the local contexts[10, 20, 23], or to health related behavior associated with low SES.

Ultimately, people interact with the health care system in the geographic areasin which they reside, and future research should assess the nature of these interactions and how they may contribute to the observed geographic variation in ACSC-related hospitalizations.

Geographic Variation in Preventable Hospitalizations Across Canada

Figure Captions

Figure 1. Age-Standardized Annualized Hospitalization Rates (quartiles) forAmbulatory Care Sensitive Conditions per 100,000 population: Canada (Census Divisions)

Figure 2. Hot Spots and Cold Spots in Preventable Hospitalizations: Canada (Census Divisions)

Note: This map identifies clusters of Census Divisions with significantly higher (hots spots) or lower (cold spots) rates of hospitalizations for ambulatory care sensitive conditions compared to their neighbors.

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Competing Interest Statement

None declared

Contributors

All authors contributed to the design of the study. PW planned and undertook statistical analysis and interpretation. PW and AM drafted and finalized the manuscript with review by SA, KA, AC, MC, SF, JG, MH, SH, SK, KN, RP, S Sarma, S Singh, S Stranges, and AT.All authors reviewed, commented on and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PW had full access to the data.

Ethics

Ethical approval for this study was not required as the study uses anonymous and confidential secondary data from Statistics Canada. Consent from respondents was obtained at the time of data collection.Data were provided by Statistics Canada through the Research Data Centres program and accessed under the *Statistics Act* of Canada. The analyses and the interpretation are the authors' alone.

Data availability statement

No data are available.

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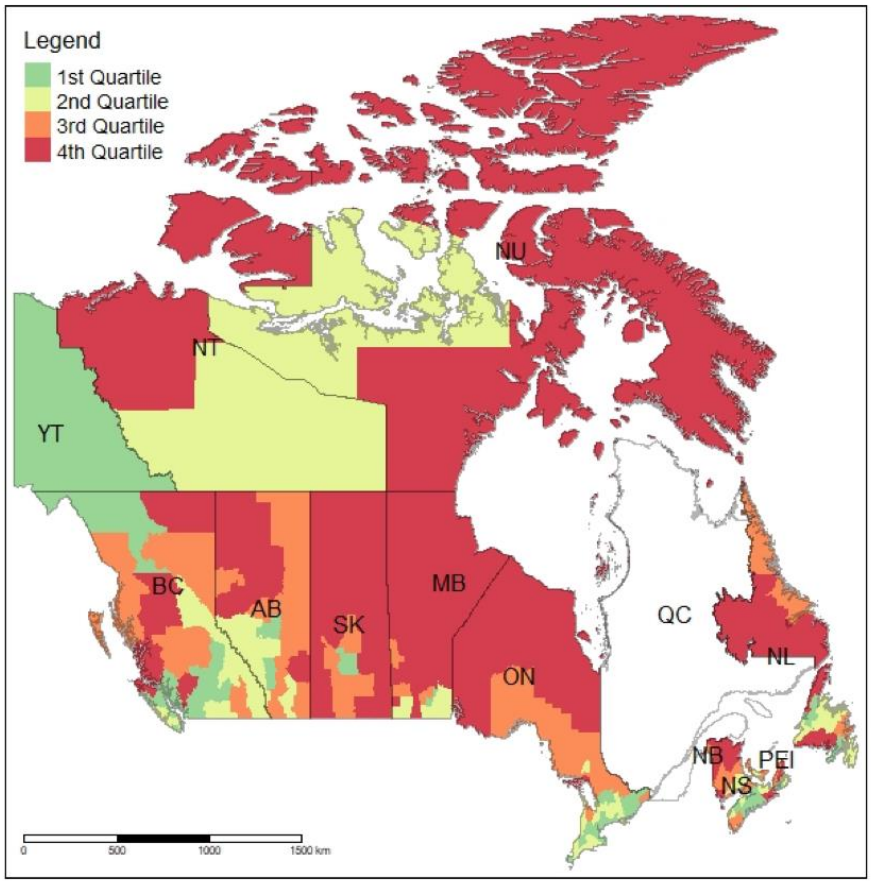

Figure 1. Age-Standardized Annualized Hospitalization Rates (quartiles) for Ambulatory Care Sensitive Conditions per 100,000 population: Canada (Census Divisions)

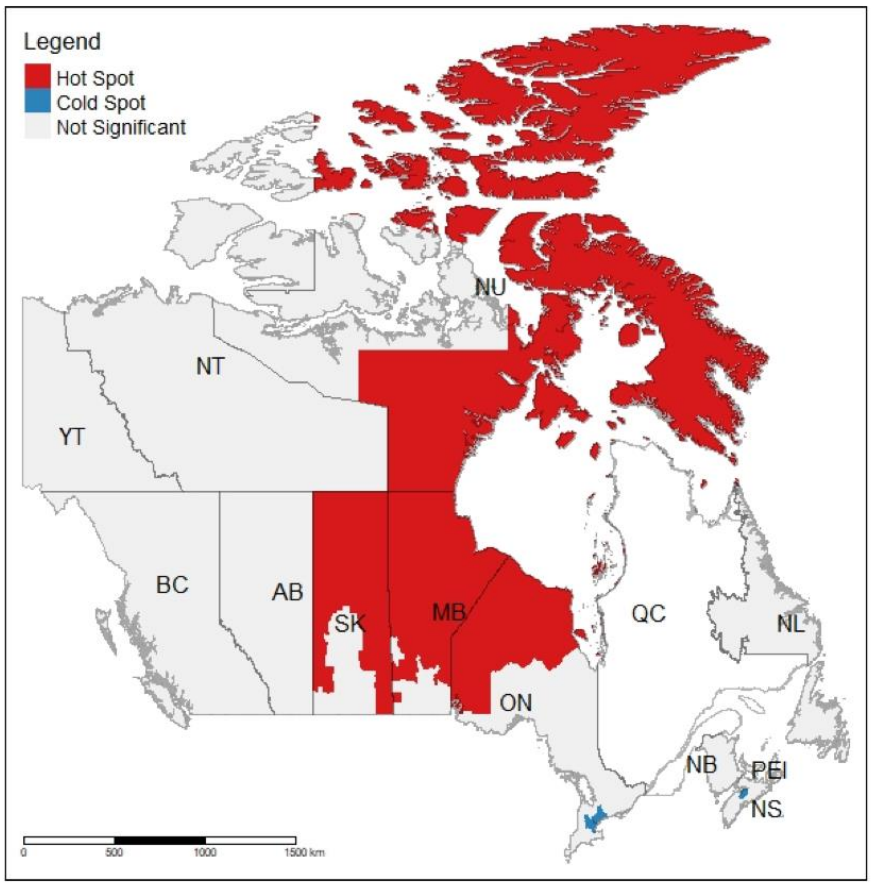

Figure 2. Hot Spots and Cold Spots in Preventable Hospitalizations: Canada (Census Divisions)

Note: This map identifies clusters of Census Divisions with significantly higher (hots spots) or lower (cold spots) rates of hospitalizations for ambulatory care sensitive conditions compared to their neighbors.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1, Line 7
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5, Lines 132-50
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6, Line 153
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6, Lines 153-59
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 6, Lines 155-60
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7, Lines 177-81
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 6, Lines 163-69; lines 183-193
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	Page 6, Lines 172-77
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7, Lines 179-93
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pages 7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page 7, Lines 184-87
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pages 8,9 Lines 220-28
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	Pages 8,9 Lines 222-43
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 10,11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12, Lines 276-91
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pages 13, 14 Lines 317-39
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 12, 13 Lines 292-316
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13, 14 Lines 332-39
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 15 Lines 364-65

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.