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Title:Geographic Clustering of Emergency Department Presentations for Acute
Coronary Syndromes and Heart Failure in Alberta, Canada: A Population-
based Study

Short Title: Geographic Clusters of ACS and HF

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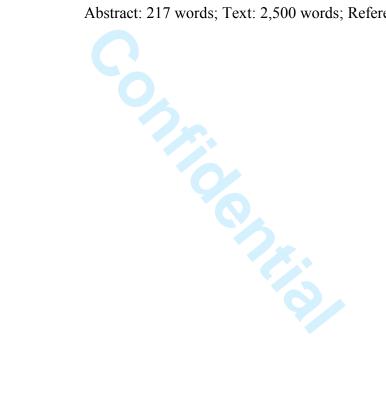
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Document:

Abstract: 217 words; Text: 2,500 words; References: 21.



<u>Abstract</u>

Background: Collectively, the most common acute cardiac presentations to emergency departments (EDs) are acute coronary syndromes (ACS) and heart failure (HF). We examine geographic variation and clustering in ED presentations by adults for ACS or HF in Alberta, Canada in 2010/2011.

Methods: All ED presentations for ACS or HF made by Alberta residents aged \geq 35 years during 2010/2011 were extracted from five linked population-based administrative health databases. Data extracted included demographics, hospitalizations, and physician claims. Spatial scan tests and logistic regression analyses were performed.

Results: There were 6,342 ACS (mean age=65.9, 63.1% male) and 4,780 HF (mean age=76.6, 49.9% male) patients. For ACS (n=6,342), a primary cluster and two secondary clusters were identified. For HF (n=4,780), a primary and two secondary clusters were also identified. Different clusters were identified for the different conditions. While primary care physician claims, prior ED visits, and prior hospitalizations were higher for patients within the high use clusters for both diagnoses, they also exhibited fewer specialist claims in the prior two years (odds ratio [OR]=0.64, 95% confidence interval [CI]: 0.56, 0.73 for ACS and OR=0.51, 95% CI: 0.43, 0.61 for HF).

Interpretation: Geographic areas were identified with higher numbers of patients presenting to the ED for ACS or HF. Lower specialist access in these areas was associated with increased ED service use.

Key Words: Acute coronary syndromes, Emergency Medicine, Heart failure, Cluster detection

Introduction

The Emergency Department (ED) is often the initial point of contact with the health care system for patients with new-onset cardiac conditions or exacerbations of chronic cardiac conditions. Collectively, the most common acute cardiac presentations to the ED are acute coronary syndromes (ACS) and heart failure (HF).(1) Overall, there is a surprisingly limited literature focusing on these important conditions in the ED setting in Canada. In particular, geographic variations have not received much attention and such variation may represent greater severity of illness, lesser availability of health care resources, variation in healthcare delivery, or a combination of these factors.

The aims of this study were to examine geographic variation in presentations made by adults (age \geq 35 years) to EDs in the province of Alberta, Canada for ACS and HF during 2010/2011.

Methods

Study Design and Setting

This study is a retrospective cohort study using population-based administrative health databases in Alberta, Canada, from April 1, 2010, to March 31, 2011.

Data were extracted from five Alberta administrative health databases: the Morbidity and Ambulatory Care Abstract Reporting (MACAR) for ED presentations, the Alberta Health Care Insurance Plan (AHCIP) cumulative registry file for population counts and demographic data, the Physician Claims File (PCF) for physician visits in non-ED settings for two years prior to the index ED presentation, the Discharge Abstract Database (DAD) for acute care hospitalizations, and Vital Statistics for death data. The MACAR database records ambulatory care visits to government funded facilities and contributes to the National Ambulatory Care Records System (NACRS).(2)

Each MACAR record represents a single ED encounter, contains a unique identifier for each Albertan, and charts are coded using the Canadian Enhancement of International Classification of Diseases, 10th Revision (ICD-10-CA)(3) diagnostic codes..

Study Protocol

The MACAR database has a main diagnosis field and nine (ICD-10-CA) additional fields for diagnosis data. To be considered a presentation, the first diagnosis field in the MACAR database had to match the diagnostic codes for ACS (I20.x, I21.x, I22, I23.82, I24.0, I24.8, I24.9, I25.0, I25.1, I25.6, I25.8, I25.9) or HF (I11.0, I50.x, J81). All ED presentations during April 1, 2010, to March 31, 2011, were extracted for Alberta residents aged \geq 35 years who matched the case definition. An ACS (HF) ED patient was defined as an individual with at least one ED presentation for ACS (HF) during the study period. ED data for April 1, 2008, to March 31, 2010, were extracted to determine if a prior history of ED presentation for ACS or HF existed. Alberta had 70 sub-regional health authorities (sRHAs, Figure 1)(4) with diverse population sizes in 2003. The geographic data provided by Alberta Health were geo-coded to the 70 sRHAs (numbered 1 to 70) and Alberta Health provided latitudes and longitudes for each sRHA's population-based centroid.

Variables for the patients included the sex, age, socio-economic proxy, and sRHA of residence at fiscal year end. The Alberta government funds health care in the province and healthcare insurance premiums provided partial funding until January 1, 2009. Residents with lower incomes or on social services (e.g., welfare) were eligible for premium subsidies. The subsidy

level can be used as a proxy measure for socio-economic status. In addition, many First Nations individuals in Alberta have "Treaty" status based on treaties between their First Nation bands and the Canadian government,(5) resulting in full premium subsidies. Combining the categories and age, we created three mutually exclusive groups: seniors (individuals \geq 65 years), subsidized adults (individuals <65 years receiving health care subsidies or who are First Nations), and non-subsidized adults (individuals <65 years who do not receive premium subsidies).

Physician claims in the two years prior to the ED presentation were extracted. The variables were date of visit, three diagnostic codes and physician specialty. Diagnoses i are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).(6) The diagnostic fields were used to determine prior histories of ACS (410.x, 411.1, 411.8, 413.x, 414.0, 414.8, 414.9, V458.8) and HF (402.01, 402.11, 402.91, 428.x, 518.4). The prior visits were also used to calculate the Charlson Comorbidity Index based on the Deyo ICD-9-CM coding scheme (hereafter called DCCI).(7) For each of the prior history and comorbidity variables, two or more physician claims in the previous two years were required to meet the definitions. Also, in the prior two years, the numbers of claims with a general practitioner and specialist (cardiology or internal medicine) were calculated. The DAD repository provided the dates of hospital admission for any reason in the two years prior to the ED presentation. Alberta Vital Statistics provided deaths within 90 days of an ED presentation.

The Human Research Ethics Board at the University of Alberta approved this study.

Analysis

For each condition, numerical summaries (e.g., frequency, mean, standard deviation [SD], interquartile range [IQR]) and crude and sex and age-group directly standardized rates (DSRs) were calculated in R.(8)

To identify geographic areas of excess numbers of patients presenting to the ED, we used the Kulldorff-Nagarwalla (KN) spatial scan test(9) that adjusts for the underlying population counts. It is a popular method for identifying clusters(10-14) and calculations were performed in SaTScan(15) with a space window of up to 50% of Alberta's population, sRHAs as the geographic boundaries, and sex and age-group as strata. The sRHA of residence was used for each patient and patients with missing sRHAs were not used in analyses. The spatial scan identifies a primary cluster (the most likely cluster that has the highest maximum likelihood ratio and rejects the null hypothesis of no clustering) and any secondary clusters (areas distinct from the primary cluster that have high maximum likelihood ratios that also reject the null). (9) Statistically significant (p-value<0.05) primary and secondary clusters were reported.

Multivariable logistic regression models were created for each condition to identify explanatory variables that differed for patients inside the statistically significant clusters. Age and sex were entered into the models even though detection was adjusted for age group and sex. Socio-economic proxy, comorbidity score, prior claims for comorbid conditions (i.e., COPD, diabetes, hypertension, kidney disease), prior ED history of ACS or HF, prior history of a hospitalization for any reason, prior history of a physician claim for ACS or HF, number of physician claims, and prior history of a specialist visit were all entered into the multivariable model. Odds ratios (ORs) and 95% confidence intervals (CIs) are provided.

Results

General Trends

Overall, 13,283 ED presentations for ACS (7,059) and HF (6,224) were extracted. Most patients (84.8%) had 1 ED presentation and 198 were identified in both cohorts. Two patients without sRHA data were removed. Analyses were conducted on 6,342 ACS and 4,780 HF patients.

The ACS group had more males, was younger, had fewer hospitalizations, had fewer physician claims, and fewer had had a prior specialist visit than the HF group (Table 1). Within 90 days of the ED presentation, 340 (5.4%) and 821 (17.2%) patients had died in the ACS and HF groups, respectively. Overall, the crude rates of patients with at least one ED presentation were 3.25 per 1,000 (95% CI: 3.17, 3.33) for ACS and 2.45 per 1,000 (95% CI: 2.38, 2.52) for HF. When adjusted by age group and sex, the DSRs ranged from 1.67 per 1,000 (95% CI: 1.27, 2.15) to 7.98 per 1,000 (95% CI 4.63, 15.10) for ACS (Figure 2). For HF (Figure 3), the lowest DSRs ranged from 0.68 per 1,000 (95% CI: 0.36, 1.18) to 6.79 per 1,000 (95% CI: 5.16, 8.96). The regions with the highest and lowest DSRs were different for ACS and HF.

Geographical Clustering

ACS

Clusters of higher numbers of patients presenting to the ED for ACS than expected were identified (Table 2, Figure 4) in the northwest (Cluster 1, the primary cluster), east central (Cluster 2) and south (Cluster 3). Cluster 1 had 926 observed patients when 619.43 were expected, adjusted for the age group and sex distribution. With an observed to expected ratio of 1.49 and a relative risk of 1.58, this collection of sRHA's was the most likely cluster (p<0.001). Clusters 2 and 3 had relative risks of 1.76 (p<0.001) and 1.47 (p<0.001), respectively.

When the primary and secondary clusters were combined, variables differed for the patients residing inside versus outside the clusters (Table 3). The clusters were less likely to have non-subsidized adults (OR=0.74, 95% CI: 0.61, 0.91) and more likely to have patients with prior hospitalization (OR=1.44, 95% CI: 1.24, 1.68) or ED presentation (OR=1.29, 95% CI: 1.04, 1.59) for ACS. They were less likely to have had a prior specialist claim (OR=0.64, 95% CI: 0.56, 0.73), had fewer specialist claims (OR=0.97 per claim, 95% CI: 0.96, 0.98) and more general practitioner claims (OR=1.01 per claim, 95% CI: 1.01, 1.01) than patients outside the clusters. Notably, 49.5% had a specialist visit in the prior two years in the clusters compared to 57.9% outside the clusters (Supplementary Table S1). Further, 8.9% of patients in the primary cluster (82/926) had at least one ED presentation that ended in admission compared to 14.0% (176/1260) and 13.2% (547/4156) in the secondary clusters and the rest of the province, respectively.

HF

The primary cluster of HF patients identified included several of the areas that were part of the primary cluster for ACS as well as the northeastern part of the province (Table 2). With 677 observed patients, the observed to expected ratio was 1.70 and the relative risk was 1.81 (p<0.001). The first secondary cluster (Cluster 2) included two sRHAs that were part of Cluster 3 for ACS. This south east portion of the province (Figure 5) had a relative risk of 1.77 (p<0.001) and Cluster 3 in eastern Alberta had a relative risk of 1.39 (p<0.003).

When adjusted by other factors, the patients in the clusters were less likely to be female (OR=0.82, 95% CI: 0.71, 0.94) and more likely to have a history of ACS (OR=1.34, 95% CI: 1.12, 1.60). Patients in the clusters were more likely to have had a prior hospitalization

(OR=1.44, 95% CI: 1.21, 1.71), more likely to have had a prior ED presentation for ACS (OR=1.49, 95% CI: 1.15, 1.92), more likely to have had a prior ED presentation for HF (OR=1.41, 95% CI: 1.16, 1.71), and less likely to have had a prior specialist visit (OR=0.51, 95% CI: 0.43, 0.61). These patients also had more physician claims (OR=1.004 per claim, 95% CI: 1.002, 1.006) and had fewer specialist claims (OR=0.98 per claim, 95% CI: 0.97, 0.98). Inside the clusters, 61.2% had had a specialist visit in the two years prior compared to 72.8% outside the clusters (Supplementary Table S2).

Interpretation

Using databases involving ACS (n=6,342) and HF (n=4,780) patients, important geographic variations were identified. Interestingly, different clusters for ACS and HF were identified, with only some sRHAs part of the clusters for both conditions. Since the risk factors for both conditions are similar, this finding would argue against regional differences in underlying risk factor distributions. Similarly, specialist access would be the same for both conditions in a geographic area. The clusters may exist because of a greater severity of disease, differences in ED management, or a lack of available non-ED health services.

Few studies have examined geographic clustering for cardiac and cardiovascular conditions. In 2010/2011, we identified clusters of patients presenting to the ED for atrial fibrillation and flutter in several sRHAs as well as clusters of these patients with a subsequent stroke or heart failure physician claims.(16) We used a different statistical cluster detection method and showed that most of the northern, some of the western, and some of the southern sRHA's were clusters alone or in combination with neighbours. van Rheenen and colleagues(12) used the spatial scan and dissemination areas to identify regional variation in ischemic stroke, transient ischemic attack,

intracerebral hemorrhage, and subarachnoid hemorrhage, and in-hospital mortality for Alberta individuals diagnosed with stroke who accessed the health care system (e.g., hospitalizations, ambulatory care including ED visits) during 2002 to 2008. They found that clusters for different conditions did not overlap. Other cluster detection studies using Alberta data have focused on different conditions. While geographic variation in admission rates or length of stay have been identified in multiple studies for ambulatory care sensitive conditions,(17) many studies do not conduct statistical cluster detection tests or consider ED visits.

This study also revealed important differences in the characteristics of patients residing inside and outside the clusters, adjusting for other variables. As expected, most of the health services usage characteristics (prior hospitalization, ED presentation, physician claims) were higher for patients residing in the clusters and these effects are likely indicative of sicker patients who see their general practitioner's more frequently and may end up presenting to the ED or admitted to hospital as they become sicker. However, the fact that patients in the cluster were less likely to have had a prior specialist claim and had fewer specialist claims is surprising if the patients are truly sicker. This result suggests that access to specialists may be reduced in some areas and gives rise to the hypothesis that earlier specialist intervention may reduce future ED presentations. Certainly, a prior natural experiment conducted in Alberta demonstrated that increasing access to specialist care for HF patients after hospital discharge was associated with statistically significant declines in rates of mortality and readmission in the first 30 days after discharge.(18) In Quebec, the association between affiliation with a specialist and ED use depended on patient age: the <65 year group had lower ED use whilst older patients had higher ED use and patients without a primary physician had more ED use than patients with a specialist primary physician.(19) While this study involved a large number of patients, the authors did not

Study limitations include the case definition may not be representative of all patients who have ACS or HF. The prior histories and comorbidities may not perfectly identify patients. For example, the recommendation for identifying patients with hypertension is "2 claims within two years or 1 hospitalization";(21) however, the data extract did not include admitting diagnosis. Proxies for SES (e.g., Aboriginal status, subsidy) may be neither sensitive nor specific. Aboriginal status includes only treaty First Nations and Inuit peoples and under-estimates indigenous peoples, since Métis and non-treaty First Nations Albertans are excluded. Finally, these databases do not provide treatment details, so clinician adherence to evidence-based management guidelines and patient adherence to such treatment, as well as characteristics like smoking history, cannot be determined. Nonetheless, we do not feel that these limitations have had a substantial effect on our findings.

In conclusion, this study showed geographic variations based on the number of people presenting to EDs for ACS or HF which was not explained by differences in demographics or comorbidities, but patients in the high cluster areas did exhibit lower rates of prior contact with specialist physicians. We hypothesize that increasing specialist access may reduce the reliance on ED services in high cluster areas, although this is a hypothesis that should be tested empirically.

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Disclosures

This study is based in part on data provided by Alberta Health. The interpretation and conclusions are contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the government nor Alberta Health expresses any opinion in relation to this study.

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8.



Tables

Table 1: Patients and population by condition and characteristics for 2010/2011.

	ACS]	HF		Population \geq 35	
	n (%)		n			n (%)	
	6,344		4,780		1,953,830		
Sex							
Female	2,340	(36.9)	2,393	(50.1)	983,570	(50.3	
Male	4,002	(63.1)	2,387	(49.9)	970,260	(49.7	
Age							
mean (SD)	65.9	(13.7)	76.6	(12.3)	54.1	(13.4	
median [IQR]	65	[77-55]	79	[86-69]	52	[62-43	
Socio-economic proxy Non-subsidized Adults	2,390	(37.7)	497	(10.4)	1,373,349	(70.3	
Subsidized Adults	704	(11.1)	349	(7.3)	169,665	(8.7	
Seniors	3,248	(51.2)	3,934	(82.3)	410,816	(21.0	
Comorbidity Score (based on ≥ 2 Physician Claims in Prior 2 Years)							
mean (SD)	1.1	(1.5)	2.3	(1.9)			
median [IQR] ≥2 Physician Claims	1	[2-0]	2	[3-1]			
in Prior 2 Years for							
COPD	1,009	(15.9)	1,669	(34.9)			
Diabetes	1,429	(22.5)	1,620	(33.9)			
Hypertension	3,270	(51.6)	2,950	(61.7)			
Kidney Disease	377	(5.9)	790	(16.5)			
ACS	2,212	(34.9)	1,570	(32.8)			
HF	788	(12.4)	2,573	(53.8)			
Hospitalization in Prior 2 Years	2,012	(31.7)	2,803	(58.6)			
ED Presentation for ACS in Prior 2 Years	602	(9.5)	399	(8.3)			

2						
3	ED Presentation for					 -
4 5	HF in Prior 2 Years	247	(3.9)	885	(18.5)	
6	Number of GP					 -
7	Claims in Prior 2					
8	Years					
9	mean (SD)	18.8	(24.0)	38.3	(39.5)	
10 11	median [IQR]	11	[23-5]	26	[52-11]	
12	Specialist Claim in	11	[23-3]	20	[32-11]	 -
13	Prior 2 Years	3,487	(55.0)	3,343	(69.9)	
14	Number of	5,487	(33.0)	5,545	(09.9)	 _
15	Specialist Claims in					
16 17	Prior 2 Years					
18	Phot 2 Tears					
19	mean (SD)	6.0	(12.6)	10.8	(18.5)	
20 21	median [IQR]	1	[7-0]	3	[13-0]	
22						-
23						
24						
25 26						
26 27						
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32 33						
33 34						
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39 40						
40 41						
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	ACS	HF		
Cluster 1 (primary)				
sRHA IDs	27, 28, 53, 56, 59, 60, 63, 64,	60, 61, 62, 63, 64, 65, 66, 67, 68, 69,		
	65, 66	70		
Population	190,646	189,63		
Observed Patients	926	67		
Expected Patients	619.43	399.3		
Observed/Expected	1.49	1.7		
Relative Risk	1.58	1.8		
р	< 0.001	<0.00		
Cluster 2 (secondar	y)			
sRHA IDs	35, 36, 38, 39, 40, 55	6, 7		
Population	67,596	58,86		
Observed Patients	441	29		
Expected Patients	257.67	173.2		
Observed/Expected	1.71	1.7		
Relative Risk	1.76	1.7		
р	< 0.001	< 0.00		
Cluster 3 (secondar				
sRHA IDs	1, 2, 3, 4, 5, 6, 7, 25	34, 35, 38, 39		
Population	158,290	45,90		
Observed Patients	819	21		
Expected Patients	581.53	154.8		
Observed/Expected	1.41	1.3		
Relative Risk	1.47	1.3		
relative relati	< 0.001	0.00		

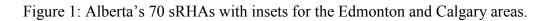
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	Ā	ACS		HF
	OR	(95%CI)	OR	(95%CI)
Sex				
Female	0.87*	(0.78, 0.98)	0.82*	(0.71, 0.94
Male	Reference		Reference	
Age	0.99	(0.99, 1.00)	0.99	(0.98, 1.00
Socio-economic proxy				
Non-subsidized Adults	0.74*	(0.61, 0.91)	0.95	(0.69, 1.30
Subsidized Adults	0.79	(0.63, 1.00)	0.98	(0.71, 1.37
Seniors	Reference		Reference	
Comorbidity Score (based on ≥2 Physician Claims in Prior 2 Years)	1.01	(0.95, 1.08)	1.02	(0.96, 1.09
≥2 Physician Claims in Prior 2				
Years for	1.02	(0.07.1.01)	1 1 7	(0.00 1.25
COPD	1.03	(0.87, 1.21)	1.15	(0.99, 1.35
Diabetes	0.94	(0.81, 1.09)	0.96	(0.82, 1.13
Hypertension	1.06	(0.95, 1.19)	1.09	(0.94, 1.26
Kidney Disease	0.91	(0.69, 1.19)	0.81	(0.64, 1.03
ACS	0.99	(0.86, 1.15)	1.34*	(1.12, 1.60
HF	1.19	(0.96, 1.48)	0.99	(0.83, 1.18
Hospitalization in Prior 2 Years	1.44*	(1.24, 1.68)	1.44*	(1.21, 1.71
ED Presentation for ACS in Prior 2 Years	1.29*	(1.04, 1.59)	1.49*	(1.15, 1.92
ED Presentation for HF in Prior 2 Years	1.08	(0.78, 1.50)	1.41*	(1.16, 1.71
Number of GP Claims in in Prior 2 Years	1.01*	(1.01, 1.01)	1.00*	(1.00, 1.01
Specialist Claim in Prior 2 Years	0.64*	(0.56, 0.73)	0.51*	(0.43, 0.61
Number of Specialist Claims in Prior 2 Years	0.97*	(0.96, 0.98)	0.98*	(0.97, 0.98

Table 3: Estimated odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models for the odds of being in the clusters.

* denotes p<0.05

Figures



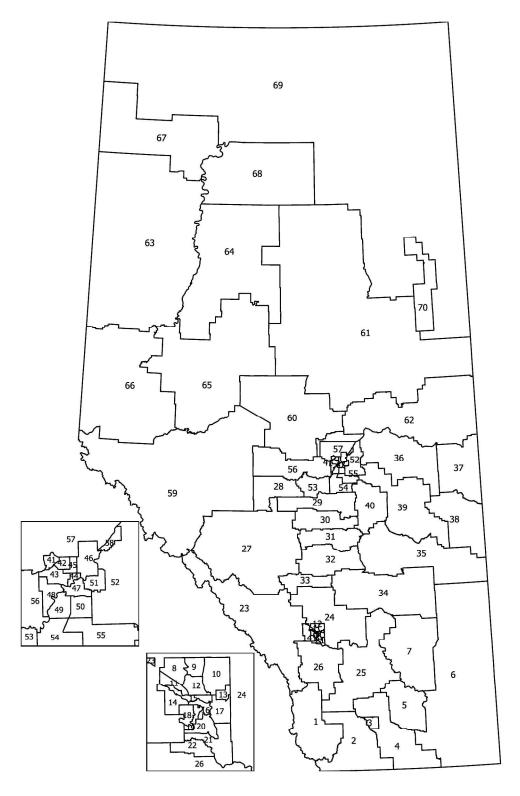
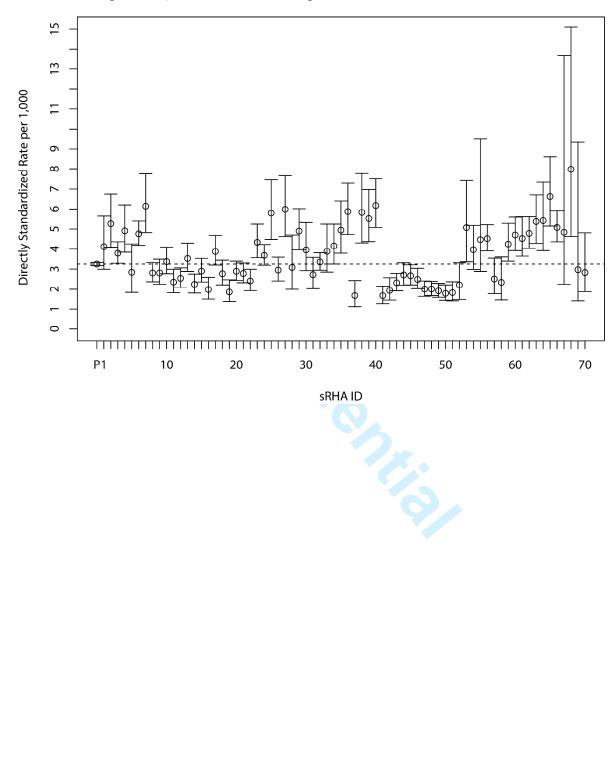


Figure 2: Age group and sex adjusted DSRs per 1,000 and 95% CIs for ACS by sRHA ID (P denotes entire province). Dotted line denotes provincial rate.



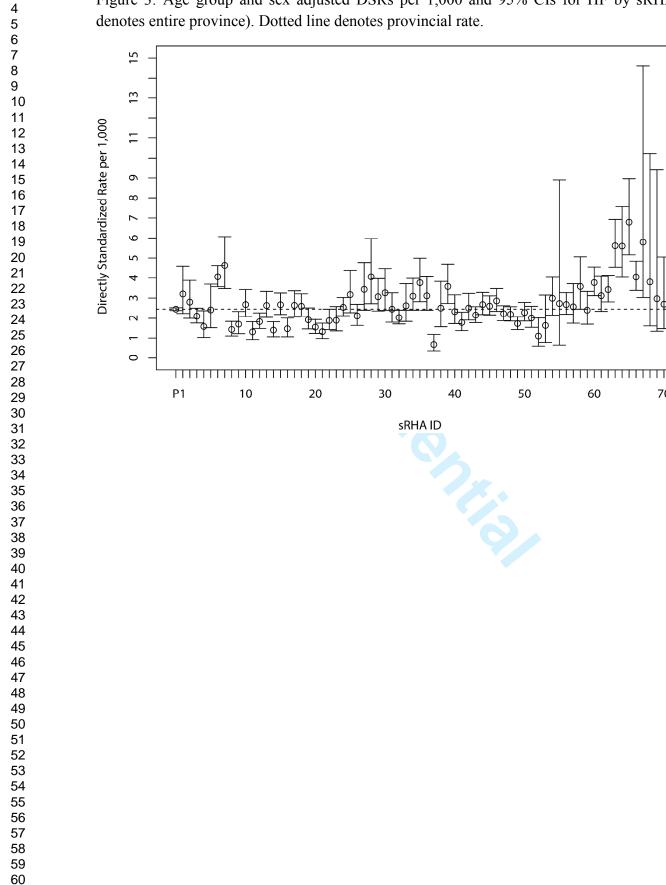
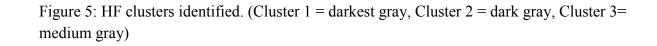
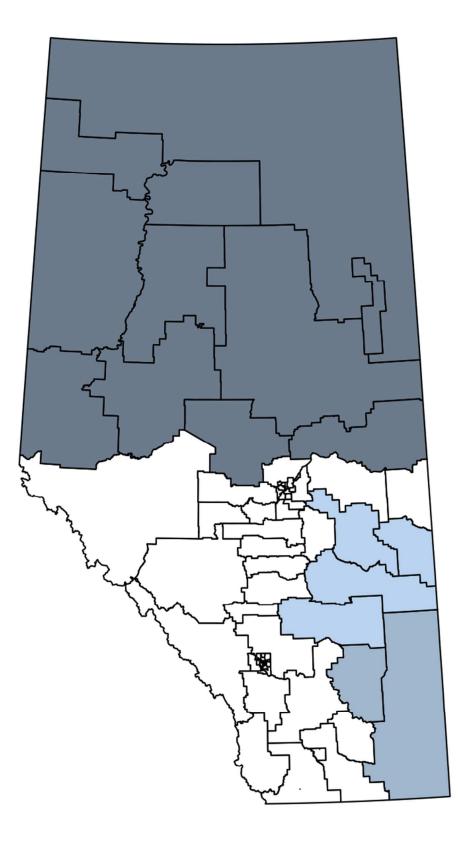


Figure 3: Age group and sex adjusted DSRs per 1,000 and 95% CIs for HF by sRHA ID (P

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Figure 4: ACS clusters identified. (Cluster 1 = darkest gray, Cluster 2 = dark gray, Cluster 3= medium gray)





STROBE Statement-checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Completed
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title	,
		or the abstract	\checkmark
		(b) Provide in the abstract an informative and balanced summary of	/
		what was done and what was found	\checkmark
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation	/
		being reported	\checkmark
Objectives	3	State specific objectives, including any prespecified hypotheses	\checkmark
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	v
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and	1
		methods of selection of participants. Describe methods of follow-up	v
		(b) Cohort study—For matched studies, give matching criteria and	
		number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential	
		confounders, and effect modifiers. Give diagnostic criteria, if	\checkmark
		applicable	
Data sources/	8*	For each variable of interest, give sources of data and details of	
measurement		methods of assessment (measurement). Describe comparability of	\checkmark
		assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	\checkmark
Study size	10	Explain how the study size was arrived at	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If	1
		applicable, describe which groupings were chosen and why	v
Statistical methods	12	(a) Describe all statistical methods, including those used to control for	~
		confounding	v
		(b) Describe any methods used to examine subgroups and interactions	✓
		(c) Explain how missing data were addressed	✓
		(d) Cohort study—If applicable, explain how loss to follow-up was	NT 4
		addressed	NA
		(<u>e</u>) Describe any sensitivity analyses	NA

Continued on next page

Results			Complete
Participants	13*	(a) Report numbers of individuals at each stage of study-eg numbers	\checkmark
		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	\checkmark
Descriptive	14*	(a) Give characteristics of study participants (eg demographic, clinical, social)	\checkmark
data		and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of	\checkmark
		interest	
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	\checkmark
Outcome data	15*	Cohort study-Report numbers of outcome events or summary measures over	\checkmark
		time	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates	\checkmark
		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	\checkmark
		(c) If relevant, consider translating estimates of relative risk into absolute risk	\checkmark
		for a meaningful time period	
Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and	\checkmark
		sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	\checkmark
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or	\checkmark
		imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	\checkmark
		limitations, multiplicity of analyses, results from similar studies, and other	
		relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	\checkmark
Other information	on		
Funding	22	Give the source of funding and the role of the funders for the present study and,	\checkmark
		if applicable, for the original study on which the present article is based	

*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.