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Clinical Research Article

Adrenal Insufficiency: Investigating Prevalence and Healthcare Utilization Using Administrative Data

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Abstract

Context: Adrenal insufficiency (AI) is an uncommon, life-threatening disorder requiring lifelong treatment with steroid therapy and special attention to prevent adrenal crisis. Little is known about the prevalence of AI in Canada or healthcare utilization rates by these patients.

Objective: We aimed to assess the prevalence and healthcare burden of AI in Alberta, Canada.

Methods: This study used a population-based, retrospective administrative health data approach to identify patients with a diagnosis of AI over a 5-year period and evaluated emergency and outpatient healthcare utilization rates, steroid dispense records, and visit reasons.

Results: The period prevalence of AI was 839 per million adults. Patients made an average of 2.3 and 17.8 visits per year in the emergency department and outpatient settings, respectively. This was 3 to 4 times as frequent as the average Albertan, and only 5% were coded as visits for AI. The majority of patients were dispensed glucocorticoid medications only.

Conclusion: The prevalence of AI in Alberta is higher than published data in other locations. The frequency of visits suggests a significant healthcare burden and emphasizes the need for a strong understanding of this condition across all clinical settings. Our most concerning finding is that 94.3% of visits were not labeled with AI, even though many of the top presenting complaints were consistent with adrenal crisis. Several data limitations were discovered that suggest improvements in the standardization of data submission and coding can expand the yield of future studies using this method.

Key Words: adrenal insufficiency, Addison's disease, hypopituitarism, healthcare utilization, quality improvement, administrative data

Adrenal insufficiency (AI) is an uncommon, life-threatening condition with a rising prevalence [1,2]. AI is the result of a deficit in the production or action of glucocorticoids [3] and with potential associated deficiency in mineralocorticoids and/or adrenal androgens. In terms of anatomical classification, primary AI is due to a defect in the production of hormones in the adrenal cortex. Primary AI can be due to various causes including autoimmune, infectious, trauma, genetic, malignancy, and drug-induced etiologies [3]. Impaired adrenocorticotropic hormone production at the pituitary or corticotropin-releasing hormone at the hypothalamus are classified as secondary and tertiary AI, respectively [3]. AI is certainly of topical concern given its rising prevalence [1,4], as well as the rising rates of opioid dependence, that have brought this etiology of central AI to the forefront [5]. There is also significant geographical variability in its prevalence: the lowest occurrence reported has been in Japan at 5 cases per million and the highest in Norway at 144 cases per million [2,6,7].

As with any medical condition, appropriate allocation of services relies on using accurate measures to understand the needs of a population [8]. The use of administrative health data has powerful potential when investigating uncommon conditions that are generally limited by recruitment and sample size in traditional or retrospective analysis studies [9]. By identifying cases using administrative health data, variations in prevalence in local areas as well as during different time periods can be estimated [9]. Thus far, there are limited epidemiological data on AI in Canada. Furthermore, intranational comparisons are limited by distinct healthcare systems in each province or territory. Studies in the United States have shown that patients with AI have higher rates of healthcare utilization compared to matched controls [10,11]. Knowledge of the local prevalence of AI, the number of services used for its treatment, and the most common reasons these patients present for care would ensure adequate resource allocation.

The primary objectives of this study were to determine the period prevalence of AI over a 5-year period (January 1, 2014 to December 31, 2018) and to determine the rates of emergency and outpatient healthcare utilization among this patient population in Alberta, Canada. Secondary objectives

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of this analysis were to describe the glucocorticoid and mineralocorticoid medication dispensation of these patients and the most common reasons for visiting the emergency department (ED) and outpatient clinics.

Methods

A population-based, retrospective, linked administrative health data approach was used to identify patients with a diagnosis of AI and their emergency and outpatient visits in Alberta between January 1, 2014, and December 31, 2018. The province of Alberta has a single public health system that collects data within the 3 sources that provided the variables for this study: the Physician Claims Database, the National Ambulatory Care Reporting System (NACRS), and the Pharmaceutical Information Network (PIN). All Albertan residents seeking care in Alberta would be captured within this provincial reporting structure. The Physician Claims and NACRS data sets were linked to PIN records using unique lifetime identifiers. A description of these databases can be found in the Supplementary Appendix S1 [12].

Case Definition for Adrenal Insufficiency

A case definition for AI, as illustrated in Table 1, was created by a group of endocrinologists and researchers based on *International Classification of Diseases*, 9th and/or 10th edition (ICD-9 and ICD-10, respectively) codes and relevant medications dispensed to estimate the prevalence of AI. The coding used was kept broad to capture all etiologies of AI.

Given the existence of the PIN database, where pharmacies in Alberta are required to register dispensed medications within 24 h, we included the dispensation of prescribed glucocorticoids and/or mineralocorticoids to the case definition. We queried the 3 databases to identify adult (aged ≥18) Alberta residents with at least 1 emergency or outpatient visit related to AI between January 1, 2014 and December 31, 2018 with the following criteria:

1. An ICD-9 diagnosis of 255.4, 255.2, or 255.5 in Physician Claims or an ICD-10 diagnosis of E27.1, E27.2, E27.3, E27.4, or E25.0 in NACRS and with at least 2 PIN dispensing records of glucocorticoid or mineralocorticoid after the earliest date of diagnosis (index date), or
2. An ICD-9 diagnosis of 253.2 in Physician Claims or an ICD-10 diagnosis of E89.3 or E23.0 in NACRS and with at least 2 PIN dispensing records of glucocorticoid after the earliest date of diagnosis (index date).

The period prevalence was calculated as the number of unique patients, identified by personal healthcare numbers, with at least 1 emergency or outpatient visit with a code for AI between January 1, 2014 and December 31, 2018, divided by the mid-interval population size of Alberta [defined as the adult (≥18 years) population of Alberta in 2016, which was 3.143995 million] [13].

Estimating Rates of Emergency and Outpatient Healthcare Utilization

The unique lifetime identifiers of the patients were used to query the Physician Claims and NACRS databases for all emergency and outpatient visits from a patient's index date to December 31, 2018. A visit was defined to be related to AI if the visit had at least 1 diagnostic code for AI associated with it.

There are 2 sources of emergency and outpatient data in Alberta: the Physician Claims database and the NACRS database. All emergency room visits are captured in the NACRS database, and most are captured in the Physician Claims database. For outpatient visits, some visits are captured in Physician Claims only, some in NACRS only, some in both, and some in neither. To count the number of unique visits, it was therefore necessary to attempt to identify and remove duplicate visits both within and between these databases. The Physician Claims database uses ICD-9 coding taxonomy, while NACRS uses ICD-10. To remove duplicate visits, we first removed duplicate visits from within each database (ie, visits with identical information). We then combined the data sets and, as there is no official reconciliation between these 2 databases, identified and removed duplicate visits between them using the following definition: a visit for the same patient on the same date with the same visit type (emergency or outpatient) and at the same facility was considered a duplicate.

The main reason for the visit was considered to be the first diagnostic code in both the Physician Claims and NACRS data sets as it is defined as the diagnosis or condition that is most responsible for the patient's visit.

Medications

The unique lifetime identifier of each patient was used to query the PIN database for glucocorticoid and mineralocorticoid medication dispenses between their index date (earliest date in the time period with a diagnostic code for AI) and December 31, 2018. The list of glucocorticoid and mineralocorticoid medications that were searched for can be found in the Supplementary Appendix S1 [12]. Each patient was categorized as having been dispensed glucocorticoid medications only, mineralocorticoid medications only, or both.

Statistical Methods

Descriptive statistics were presented as frequencies and percentages as well as means and SDs. Results were stratified by whether the visit was related to the treatment of AI, where applicable. For descriptive purposes only, 2 bivariate ordinary least squares regression lines of best fit were calculated to depict the overall trend in visit rates over the time period; ED or outpatient visit rates were the dependent variables (y) and year (2014-2018) was the independent variable (x) in each calculation. Additionally, for descriptive purposes, we conduct inferential tests to determine whether there are differences in visit rates across years based on emergency or outpatient settings.

Results

Period Prevalence of AI

Over the 5-year period, 2637 patients were recorded to have made an outpatient or ED visit related to AI. Using the defined case definition (Table 1), the estimated prevalence of AI was 0.0839%, or 839 per million persons, in Alberta between 2014 and 2018.

Healthcare Utilization

Number of visits made by patients with AI

Patients with AI made a total of 211 207 emergency and outpatient visits for any reason. Out of these visits, 5.7% (n = 12 060) were

Table 1. Case definition for adrenal insufficiency

At least 1 of the following from either database:		**AND At least 2 separate dispenses of any of the following medications:**
Physician Claims Database	NACRS	PIN
ICD-9 diagnosis codes: • 255.41 – glucocorticoid deficiency • 255.5 – other adrenal hypofunction • 255.2 – adrenogenital disorders (includes congenital adrenal hyperplasia) • 255.4 – corticoadrenal insufficiency • 253.2 – panhypopituitarism	ICD-10 diagnosis codes: • E27.1 – primary adrenocortical insufficiency • E27.2 – Addisonian crisis • E27.3 – drug induced adrenocortical insufficiency • E27.4 – other and unspecified adrenocortical insufficiency • E25.0 – congenital adrenogenital disorders associated with enzyme deficiency • E89.3 – postprocedural hypopituitarism • E23.0 – hypopituitarism	Glucocorticoids: • Betamethasone • Dexamethasone • Fluocortolone • Methylprednisolone • Paramethasone • Prednisolone • Prednisone • Triamcinolone • Hydrocortisone • Cortisone • Prednylidene • Rimexolone • Deflazacort • Cloprednol • Meprednisone • Cortivazol Mineralocorticoids: • Fludrocortisone

Abbreviations: ICD-9, International Classification of Diseases, 9th edition; ICD-10, International Classification of Diseases, 10th edition; NACRS, National Ambulatory Care Reporting System; PIN, Pharmaceutical Information Network

recorded as being related to the treatment of AI. Table 2 illustrates the frequency of outpatient and emergency healthcare utilization visits made by patients with AI and for the subset of visits made by these patients with a code for AI. Of the visits for any reason, 98.6% (n = 208 199) were outpatient visits. Of the 12 060 visits related to AI, 87.9% (n = 10 596) were outpatient visits.

Visit rates

Figures 1 and 2 display the rate of emergency and outpatient visits per patient over time with arrows indicating the percentage change in visit rates between each year. Patients with AI made an average of 2.26 (SD = 0.13) and 17.82 (SD = 4.40) visits per patient per year for the treatment of any reason in the emergency and outpatient settings, respectively.

Outpatient visits for any reason

The line of best fit for outpatient visits in Figure 1 depicts that outpatient visits per patient per year for any reason have been generally increasing over time among this patient population ($P < 0.01$). The rate of increase has been slowing over time, as indicated by the arrows in Figure 1.

Emergency visits for any reason

The line of best fit for emergency room visits in Figure 1 depicts that emergency visits per patient per year for any reason have remained relatively stable over time ($P = 0.59$). On average, there was an increase of 0.03 emergency room visits per patient each year over the time period.

Visits coded for the treatment of AI

Patients with AI made an average of 0.13 (SD = 0.01) and 0.91 (SD = 0.07) visits per patient per year for the treatment of AI in the ED and outpatient settings, respectively.

Outpatient visits for the treatment of AI

As shown in Figure 2, the overall trend in outpatient visits per patient per year related to the treatment of AI is that these visits have been increasing over time ($P < 0.05$). The magnitude of the increase in visits per patient per year, however, was small (increasing by 0.04 visits per patient per year, on average).

Table 2. Outpatient and emergency visits made by patients with adrenal insufficiency

	Outpatient	**Emergency**
All visits, n (%)	208 199	3008
(n = 211 207)	(98.6)	(1.4)
Visits for AI, n (%)	10 596	1464
(n = 12 060)	(87.9)	(12.1)

Abbreviation: AI, adrenal insufficiency.

Emergency visits for the treatment of AI

As shown in Figure 2, there have been small fluctuations in the number of emergency room visits per patient over time. The overall trend, however, has remained relatively stable ($P = 0.62$).

Top 10 reasons for visiting the ED

There were 2699 different main reasons for visiting the ED. Table 3 illustrates the top 10 reasons patients with AI visited the ED over this time period.

Top 10 main reasons for outpatient visits

There were 4821 different main reasons for outpatient visits. Table 4 illustrates the top 10 main reasons patients with AI visited an outpatient clinic over the time period.

Medications

Most patients with AI were dispensed only glucocorticoid medications over the time period (71.6%, n = 1889). Nearly one third (27.4%, n = 722) of patients with AI were dispensed

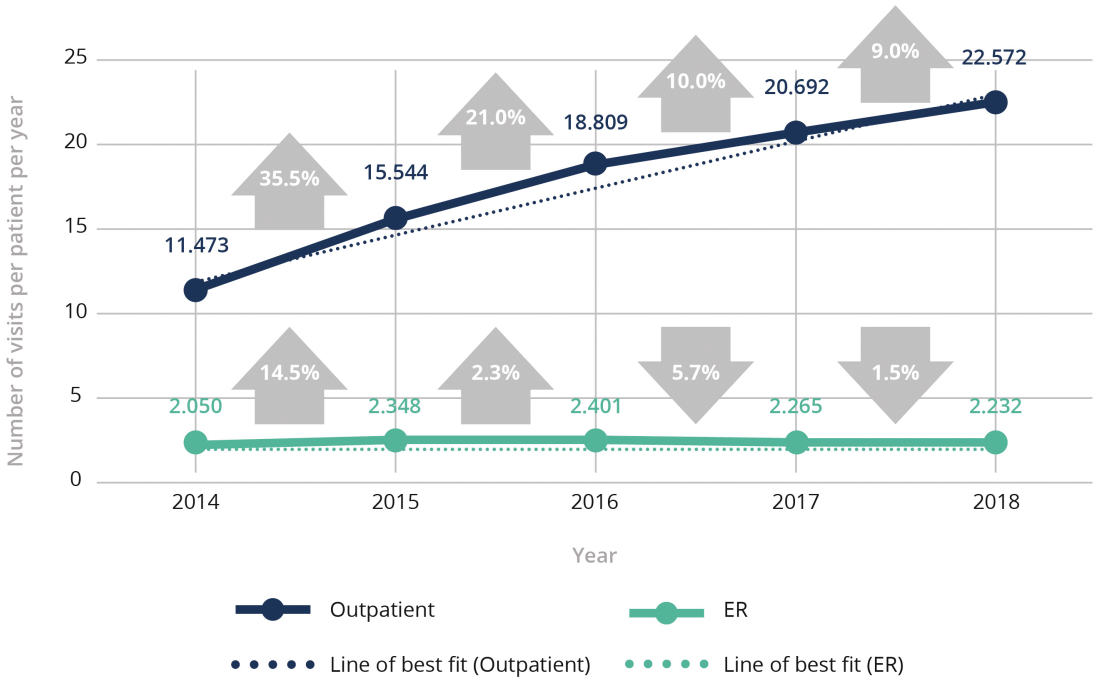

Figure 1. Emergency and outpatient visit rates for any reason by patients with AI.

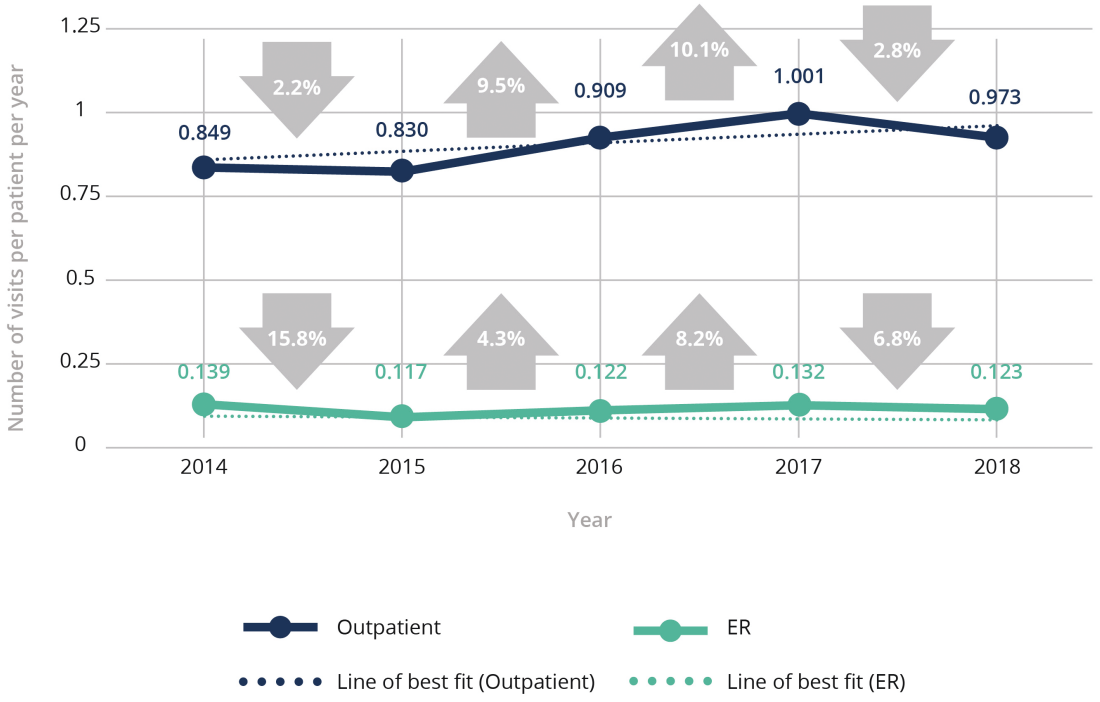

Figure 2. Emergency and outpatient visit rates for the treatment of AI.

both glucocorticoid and mineralocorticoid medications, and a small proportion (1.0%, n = 26) were dispensed only mineralocorticoids over the time period.

Discussion

To the best of our knowledge, this is the first study of its kind evaluating the prevalence, healthcare utilization, and medication dispensation records of patients with AI in Canada. Several noteworthy findings were obtained from this study. First, the period prevalence of AI in Alberta was found to be relatively high at 839 cases per million people between 2014 and 2018 when compared to other studies. Second, patients with AI made more outpatient and emergency room visits than the average Albertan [14] and the number of outpatient visit rates appear to be rising, but notably the majority of visits were not identified as related to AI. Last, the majority of patients appear to be prescribed a glucocorticoid only during

this time frame. Our findings provide a framework for using healthcare administrative data to analyze clinical trends for an uncommon condition in a population.

In keeping with previous literature, our findings reiterate the uncommonness of AI—an aspect that often makes it difficult to determine general population-level trends and clinical effects of treatment [6]. On a global level, the reported prevalence in European and Western countries is estimated at around 100 per million and 39 to 144 per million, respectively, while the highest reported has been Norway with 144 per million [6,15,16]. In comparison, the period prevalence of AI found by our analysis in Alberta is relatively high and raises questions as to the origin of this disproportionate burden. There are various factors that should be considered when analyzing the cause of increased burden. For primary AI, it is clear that the rates of autoimmune adrenalitis in developing countries have been rising and other risk factors such as sex (female predominance), ethnicity (white/Caucasian), and age (most often 30-50 years of age) impart an increased risk [3]. Overall it is unclear what has resulted in this high prevalence in Alberta's population as demographic data were not available for analysis. Future analyses will investigate these considerations. Furthermore, several caveats to our obtained data likely render the period prevalence an underestimation, which further raise concern about the true burden of AI on healthcare utilization. These include variable mandatory coding requirements by health system payers, inconsistent outpatient data submission and reporting to administrative databases, and the need for manual reconciliation of databases [17,18]. The period prevalence may be underestimated because it is possible that not every patient with AI in Alberta will have visited an ED or outpatient clinic during the time period studied. It is also important to consider that patients may have not had a visit coded for AI during the time period or none of their outpatient visits were submitted to NACRS or Physician Claims. Although reconciliation was required to identify duplicate visits between databases, it is unlikely that this played a role in overestimating the period prevalence as this was completed by identifying unique instances of personal health care numbers across the visits. If there were duplicate visits from the same patient, their personal healthcare number would only be counted once. Thus, it is more likely the period prevalence was influenced by coding requirements, which would overall contribute to underestimation.

Table 3. Top 10 reasons patients with adrenal insufficiency visited the emergency department, 2014-2018

Main reason for the visit	n (%)
Z51.2 - Other chemotherapy	1594 (6.1)
789.00 – Abdominal pain, unspecified site	573 (2.2)
276.5 – Volume depletion disorder	461 (1.8)
D84.1 – Defects in the complement system	390 (1.5)
995.1 – Angioneurotic edema not elsewhere classified	373 (1.4)
276 – Disorders of fluid electrolyte and acid-base balance	339 (1.3)
R104 – Other and unspecified abdominal pain	334 (1.3)
786.5 – Chest pain	312 (1.2)
780 – General symptoms	312 (1.2)
682 – Other cellulitis and abscess	255 (1.0)

Table 4. Top 10 reasons patients with adrenal insufficiency visited outpatient clinics, 2014-2018

Main reason for the visit	n (%)
Z01.6 – Radiological examination, not elsewhere classified	7990 (4.0)
Z501 – Other physical therapy	5201 (2.6)
Z718 – Other specified counseling	4628 (2.3)
780 – General symptoms	4294 (2.2)
Z491 – Extracorporeal dialysis	4158 (2.1)
255.4 – Corticoadrenal insufficiency	4043 (2.0)
Z71.9 – Counseling, unspecified	2994 (1.5)
Z51.2 – Other chemotherapy	2912 (1.5)
250 – Diabetes mellitus	2873 (1.5)
Z509 – Care involving use of rehabilitation procedure, unspecified	2785 (1.4)

Our most concerning finding is that 94.3% of visits were not labeled with AI, even though many of the top presenting complaints (eg, abdominal pain, unspecified site; volume depletion disorder, etc.) were consistent with adrenal crisis. Given that AI is typically a lifelong condition that requires stress dosing of glucocorticoids for physical stressors such as fever, surgery, and pregnancy, it is virtually impossible that 94.3% of clinic and hospital visits were not influenced by the presence of AI. Unfortunately, we could not use chart review to audit these cases, but this low rate of AI coding begs the question of whether the treating clinicians were aware of the AI diagnosis and properly managed it. This is substantiated by the fact that healthcare utilization for AI patients was higher in ED and outpatient settings. Comparing data from Alberta Health Services in 2015-2016, our findings show overall that patients with AI had 3 times as many outpatient visits (17.82 vs. 5.34) and 4 times as many ED visits (2.26 vs 0.52) per person per year when compared to the average Albertan [14], providing even more evidence that AI was underreported as an associated diagnosis. This is in agreement with Gunnarsson et al, who showed similar substantially increased annual healthcare burdens for patients with AI in the United States [10].

Primary AI results in impairment of all adrenal axes whereas in secondary AI, the mineralocorticoid axis is still usually intact [19]. It is expected that primary AI patients be prescribed a combination of glucocorticoid and mineralocorticoid replacement whereas secondary AI patients would require glucocorticoid replacement only [3,6,19,20]. Although the majority of patients in our study were prescribed only glucocorticoid medication (71.6%) or combination glucocorticoid and mineralocorticoid (27.4%), we do not have enough definitive data to draw conclusions about the etiology of AI. Of note, the ICD-10 code E27.3 (drug-induced adrenocortical insufficiency) included various agents such as antibiotics/antifungals, opioids and other analgesics, and other systemic therapies. Unfortunately, we did not have subcategorized "cause codes" to detail specific drugs and frequency of occurrence to supplement these data. Björnsdottir et al had previously shown via a population-based cohort study in Sweden how prescription patterns can be used to analyze AI and associated comorbidities [6]. Beyond epidemiological measures, studies like Eyal et al's assessment in a pediatric population brings to light how determining the underlying etiology may help anticipate the percentage of patients at highest risk for

adrenal crises as well [21]. Ideally, future studies of medication dispensation records linked to detailed medical records will enable better understanding of a patient's risk for future crises and complications and enable preventive approaches.

Several limitations to this methodology and study must be addressed. First, as mentioned previously, results are contingent upon the claims and NACRS data submitted, as well as coding practices. It is not mandatory in Alberta for all outpatient visits to be submitted and entered into an administrative database; therefore, some visits may be missed using this method [17]. Furthermore, it is not mandatory to submit outpatient visits to NACRS, and physicians on alternative payment plans are not mandated to submit to Physician Claims. Minimal coding requirements in Alberta, in which only a single code per visit must be submitted, with the use of nonspecific codes, such as "follow-up" without other medical diagnosis, may underrepresent capture of AI presentations and diagnoses. Second, this method can provide population-level estimates but is not able to rationalize findings to the individual patient care level without supplemented information through chart review. Third, as studies on the epidemiology of AI in Canada are limited, a comparator group could not be established. Overall it is clear that using this methodology requires a strong understanding of local coding and data submission processes. Future efforts in building more specific case definitions and integrating information with electronic medical records data may also help provide clarity.

In conclusion, our results show that although AI is an uncommon diagnosis, it appears to have a higher prevalence in Alberta than reported in other studies. It is unclear what etiological factors may be responsible for this relatively higher prevalence. Furthermore, patients with AI access care much more frequently than the average Albertan. With rising outpatient visits, the care demands are expected to increase in the coming years. While there appear to be various reasons for patients presenting to medical attention that are not coded specifically for AI, we do suspect that if these visits were to be closely examined, a number likely include adrenal crisis given AI's broad range of clinical presentations as well the use of nonspecific ICD codes and minimal coding requirements. This is the first study of its kind to evaluate AI in Canada specifically using administrative data. Future studies could add further light to these findings by broadening the scope of administrative data obtained, supplementing data with chart review and hospital records, and utilizing this methodology in other provinces to generate comparative data.

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Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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