A Population-Based Retrospective Cohort Study of Pediatric Diabetic Ketoacidosis (DKA) Hospital Admissions in Northern and Southern Ontario: Do Geography and Physician Diabetes Care Matter?

By

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Abstract

Background: Diabetic Ketoacidosis (DKA), an acute complication of diabetes, is a major cause of death and disability in children with diabetes. The main purpose of this study was to describe the prevalence of DKA hospital admissions in Ontario children with diabetes and examine how it is associated with children's geographic location and use of physician diabetes care services. The secondary purpose was to describe trends in pediatric diabetes incidence in Northern and Southern Ontario and the entire province.

Methods: A population-based retrospective cohort design included all Ontario children (younger than 18 years old) diagnosed with diabetes (type 1 and 2 combined) from 2004 to 2012 (n=10,617). Person-level health administrative records of hospital admissions for DKA from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database were linked to the records of diabetes related physician visits from the Ontario Health Insurance Plan (OHIP) database and emergency department visits from the CIHI National Ambulatory Care Reporting System. The person-level linked dataset for the study cohort was created at the Institute for Clinical and Evaluative Studies (IC/ES).

Results: Background statistics on pediatric diabetes in Ontario indicated a declining incidence trend in 2009-2012. There was evidence of regional differences in DKA hospital admission prevalence, pediatric incidence, and patterns of physician diabetes care services use between Northern and Southern Ontario. Northern Ontario children had higher diabetes incidence; poorer access to pediatric endocrinologists and pediatricians; higher proportion of children without a main physician provider for diabetes care; and, higher prevalence of DKA hospital admissions in

the course of diabetes. There was a significant preventive effect of subspecialist care on DKA hospital admissions, particularly for children with diabetes and comorbidities. Groups with an increased risk of DKA hospital admission included children (0-6 years old) in the most materially deprived neighbourhoods; adolescent boys (13-18 years old); and, rural children with diabetes and mental health needs.

Conclusions: The study findings have implications for health policy ensuring equitable access to pediatric diabetes care across Ontario; targeted prevention of acute diabetes complications; and, ultimately, for quality of diabetes care and improvement of health outcomes for children with diabetes in the province.

Keywords

Diabetes ketoacidosis; Hospital admission; Subspecialist care; Pediatric diabetes; Pediatric diabetes incidence; Diabetes care; Diabetes-related physician visits; Health services; Ontario; Northern Ontario; Southern Ontario; Health administrative data; Person-level; Population-based; OHIP; CIHI-DAD; CIHI-NACRS.

Co-Authorship Statement

The three papers included in this thesis manuscript were co-authored by Oxana Mian, PhD candidate, Dr. Elizabeth Wenghofer, PhD supervisor, and committee members Dr. Nancy Young and Dr. Liisa Jaakkimainen. A draft of each paper was completed by Oxana Mian with commentaries and edits provided by the co-authors.

Disclaimer

This study made use of de-identified data from the Institute of Clinical Evaluative Sciences (IC/ES) Data Repository, which is managed by the IC/ES with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by IC/ES or any of its funders or partners is intended and should be inferred. Parts of this material are based on data and information compiled and provided by Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the authors, and not necessarily those of CIHI.

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Introduction

Pediatric diabetes is on the rise worldwide.[1-5] Comprehensive diabetes care involving pediatric physician specialists (e.g., pediatric endocrinologists or pediatricians with additional experience in pediatric diabetes) is crucial for management of this disease.[6,7] Prevention of acute complications, which may have negative effects on children's health carried into later life, is the main goal of diabetes management.[6,7] Excessive medical expenditures associated with acute diabetes complications represent a substantial burden on health care.[8,9] One of the most serious and life-threatening diabetes complications and the leading cause of mortality and disability in the pediatric diabetic population is diabetic ketoacidosis (DKA).[10] Worldwide, frequency of DKA varies from 14% to 80% at the time of diabetes diagnosis among children, and from 1 to 15% in children with established diabetes per year.[11]

Among developed countries, Canada has one of the lowest frequencies of pediatric DKA at diagnosis (18.6%).[12] However, there are geographic disparities in the overall rates of pediatric DKA within country.[13,14] Specifically, in the province of Ontario, there was almost a four-fold difference in pediatric DKA rates between Northern Ontario and other Ontario regions in 1991-1999. [13,14]A 2017 Ontario study also found a geographic disparity between rural and urban children in diabetes-related hospitalizations, which has increased between 2001 and 2011 despite an observed reduction in the socioeconomic disparity in the risk of diabetes-related acute complications associated with the implementation of the Ontario Pediatric Diabetes Network (OPDN) in 2001.[15] High rates of potentially preventable acute complications such as DKA in some regions may indicate that children in these regions have a disproportionate burden of

diabetes. They may, possibly, also indicate a problem with access to diabetes care that they need.[1] These are important and alarming findings that warrant attention from researchers and health care decision makers and planners.

My literature review (in the next chapter) presents the incidence of pediatric diabetes in Canada in 2008/2009.[16] I was unable to identify any updates since this time.[16] It is also unknown whether differences in pediatric DKA rates between Northern Ontario and other regions persisted throughout time. Furthermore, clinical standards of diabetes management in children are well developed[17] and it is agreed that prevention of DKA and reduction of its incidence should be a goal in managing diabetes in children.[18] However, there is not enough empirical evidence regarding the effects of children's use of pediatric diabetes health services on hospital admissions for acute diabetes complications (including DKA), that is an understudied topic both in Canadian and in the international literature. The main purpose of my study was to address these knowledge gaps by examining interrelations between geographic location, use of pediatric diabetes care and DKA hospital admissions in Ontario. Findings of this study may inform health care policy aimed to reduce inequities in health care access for children with diabetes in Ontario and improve health outcomes for this vulnerable population.

Key concepts

Key concepts in my study were: childhood diabetes, pediatric diabetes care, DKA, rural, and northern.

Childhood diabetes

Diabetes (short form of the medical term "diabetes mellitus") is the most common chronic condition in children after asthma and neurodevelopmental conditions.[17,19-21] It occurs when the

body cannot produce the essential hormone insulin or use insulin effectively.[22] Insulin transports glucose from the bloodstream into the body's cells where the glucose is converted into energy. The lack of insulin or the inability of the cells to respond to insulin leads to high levels of glucose in the blood stream, or hyperglycaemia. Hyperglycaemia may lead to cardiovascular disease, neuropathy, nephropathy and eye disease, leading to retinopathy and blindness, but these serious complications can be delayed or prevented with appropriate and early management of diabetes. There are three main types of diabetes, type 1 diabetes (T1D), type 2 diabetes (T2D) and gestational diabetes. In this study, I will focus on T1D and T2D in children. T1D occurs most frequently in children and adolescents.[17] It is caused by an autoimmune reaction, where the body's immune system attacks the insulin-producing beta cells in the islets of the pancreas gland. As a result, the body produces none to very little insulin leading to a relative or absolute deficiency of insulin. People with T1D need daily insulin injections to manage their glucose level and without insulin would not be able to survive. In T2D, hyperglycaemia is the result of an inadequate production of insulin and inability of the body to respond fully to insulin, defined as insulin resistance. T2D is most commonly seen in older adults, but it is increasingly seen in children, adolescents and younger adults due to rising levels of obesity, physical inactivity and poor diet.[19]

Pediatric diabetes care

According to the Canadian and international clinical practice guidelines (CPGs), there is a strong consensus that all children with diabetes should have access to an interdisciplinary pediatric diabetes healthcare team led by "a pediatrician specialized in diabetes or endocrinology (preferred); or, a physician with a special interest (and training) in childhood and adolescent

diabetes". [6,7,23,24] In order to meet the complex needs of a child with diabetes, the team should also include a diabetes nurse specialist, a dietitian or nutritionist, a social worker trained in childhood diabetes, and/or a psychologist with knowledge of childhood diabetes and chronic illness.[23] According to the CPGs, standards of care should include four routine physician visits, at least one visit with a dietitian, one visit with a behavioral specialist, and four HbA1c analyses per year.[6,7,23,24] These visits should include a review of diabetes management and home management records, an evaluation of a child's growth, development, and general health.[23] Annually, there should be an assessment of dietary knowledge; self-management skills and behaviours, and psychosocial needs; screening for comorbidities and risk factors for long-term complications; identification of barriers to care; and, educational updates. This comprehensive diabetes care model is the gold standard in Canada and in other developed countries.[23] Because of availability of centralised administrative data on physician services and the lack of similar data from other health providers, the focus of my thesis work was on children's use of diabetes care provided by physicians, with attention to the physician's specialty and frequency of physician visits for diabetes care.

Diabetes ketoacidosis (DKA)

Clinically, DKA results from a shortage of insulin and a subsequent reaction of body in producing high levels of blood acids (ketones). If untreated, this acute condition rapidly leads to coma and even death.[10,18] Because DKA is preventable with a timely diagnosis of diabetes[25] and, later, with optimal diabetes management,[26] its occurrence is a good indicator of barriers to timely and efficient access to health care for diabetes diagnosis and/or suboptimal quality of diabetes care in the course of this chronic disease. Furthermore, medical treatment of the majority of

children with moderate DKA and all children with severe DKA is required hospitalizations.[2,3] This makes this condition easily detectable in the hospital administrative data that is systematically collected by Ontario provincial government. In my study, I focused on DKA episodes that required hospital admissions, which most probably represented moderate or severe cases of DKA that potentially could have had the most detrimental effects on children's health.[2,3]

Concept of rural

In this study, I used the Statistics Canada's "rural and small town" (RST) definition that uses census subdivisions (approximating a "community") as the smallest geographic units and considers a degree of integration of rural communities with larger urban centres.[27] These features make the RST definition the most suitable for rural health services research compared with other rural definitions (e.g., census rural or rurality index for Ontario).[27] According to the RST definition, rural area is defined as all area outside urban areas, formed by Census Metropolitan Agglomerations (CMAs) and Census Agglomerations (CAs).[27] A CMA must have a total population of at least 100,000 of which 50,000 or more must live in the core formed by one or more adjacent municipalities.[28] A CA must have a core population of at least 10,000. Rural communities have population of less than 10,000 and are classified into four types or metropolitan area influenced zones (MIZs) depending on the size of commuting labour flows to the urban areas: strong MIZ (30% or more of the workforce), moderate MIZ (5 to 29%), weak MIZ (less than 5%), and no MIZ (no commuting residents).[28] In rural areas, barriers to health care most commonly include long distance to health care facilities, overall limited access to specialists such as pediatricians, endocrinologists, allied health workers (dietitians, social workers), and minimal exposure to diabetes education.[29-31]

Concept of northern

Northern Ontario was defined as the area comprising of North West and North East Ontario Local Health Integration Networks (LHINs) (Figure 0-1). Northern Ontario covers 802,846 square kilometres, representing 88% of the Ontario land, and it is populated by only 5.8% of the province's total population (780,140 of 13,448,494 people) according to the 2016 Census.[32,33] A low population density (0.97 person per square kilometre) and vast distances separating communities create unique challenges for health services planning and delivery.[34,35] Northern Ontario has a high proportion of Indigenous peoples (16.5% compared to 2.8% in Ontario).[32,33] Northern Ontario is also a home to a large Francophone population that constitutes about 15.2% of the region's population (20.8% of population in the North East LHIN) compared to 3.8% in Ontario.[32,33]

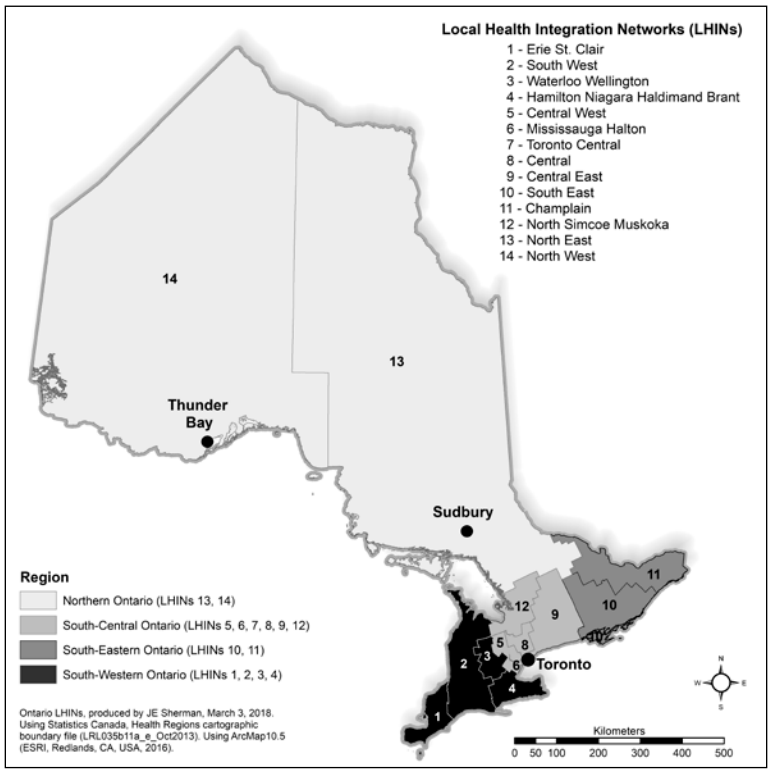

Figure 0-1: Ontario regions by LHIN

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Chapter 1

Literature review

In this chapter, I will provide a brief overview of literature concerning pediatric diabetes incidence, characteristics of pediatric diabetes care; and DKA prevalence, time trends and factors in Canada and Ontario to support my research rationale.

1.1 Incidence of pediatric diabetes in Canada and Ontario

In Canada, diabetes surveillance data indicated that in 2008/09 the pediatric diabetes incidence was 40/100,000 (or, 3,287 new cases of diabetes) and the total number of children with diabetes (0-19 years) was close to 26,000 (a prevalence rate of 0.3%).[1] Canada has one of the highest incidence rates of T1D in the world.[2] It is estimated that about 90% of diabetes cases in children are T1D, which is also referred to as "insulin-dependent diabetes mellitus."[3] T2D has historically been viewed as an adult disease (more than 90% of all Canadian people with diabetes have T2D),[4] but has been rising in children and youth over the last two decades.[5-8] In Canada, the incidence of T2D in children was 1.54 cases per 100,000/year in 2006-2008.[5] Unique to the Canadian population, 8% of children with T2D were found to be younger than 10 years of age compared to 3.6% in the U.S. pediatric population.[9] In Ontario, the most recently published data on incidence of pediatric diabetes in children (0-19 years) was 32.3/100,000 in 2003 with an average rate increase (ARI) of 3.1% from 1994 to 2003 for both diabetes types combined.[10] With a steady increase of incidence of both types of diabetes in children and youth, improvement of quality of care and health outcomes for pediatric diabetic population will remain an important concern in the future years.[11-13]

In the following section, I will review literature concerned with pediatric diabetes care in Canada and Ontario. I will further use the term "diabetes" whenever the reviewed study did not distinguish between T1D and T2D. Whenever possible, I will specify the diabetes type (T1D or T2D).

1.2 Pediatric diabetes care in Canada and Ontario

The standards of pediatric diabetes care are well established in CPGs both nationally and internationally.[14,15] However, despite the universal health care system, Canadian studies have found variation in quality of pediatric diabetes care dependent on the child's place of residence,[16] physician diabetes care provider,[16] and material deprivation.[17,18] In British Columbia, a population-based study revealed regional variation in adherence to CPGs among children with T1D[16] as well as an overall poor adherence level in children with T1D and T2D.[16,19] Thus, children residing closer to a provincial pediatric tertiary hospital were more likely to receive care recommended by CPGs than children residing further from the tertiary hospital.[16] Overall, only 54% of person-years in pediatric population with T1D[16] and less than 30% in pediatric population with T2D[19] had received recommended diabetes care. The study also reported that children seeing only general physicians (GPs) for diabetes care had lower adherence to guidelines compared to those having specialists only (i.e., general pediatricians, pediatric endocrinologists, adult endocrinologists, internist) or a combination of GP and specialist visits.[16] Research in Quebec and Ontario found significant differences in average glucose blood levels between children from the least and most deprived areas of Montreal[17] and Toronto.[18] Although these studies were limited to two metropolitan areas and may not be extended to the complete pediatric diabetic populations in the provinces, they did point out the existence of the adverse effect of deprivation on diabetes management in Canadian children with diabetes.

In Ontario, more than 90% of children and youth with diabetes receive specialized care services through the OPDN which was established in 2001.[20] The number of the OPDN patients in the 2012/2013 fiscal year was 7,215 (6,624 with T1D, 432 with T2D; 159 with 'other' types).[21] The OPDN consists of 30 secondary level specialized pediatric diabetes centres (PDCs) linked to five tertiary PDCs. Each PDC has a multidisciplinary core team of registered nurses, dietitians, and social workers, working closely with affiliated physicians. However, there is a variation in availability of pediatricians and pediatric endocrinologists across PDCs. In 20 (67%) secondary PDCs the affiliated physicians were general pediatricians, and in 4 (13%) secondary PDCs the affiliated physicians were both pediatricians and pediatric endocrinologists. Four (80%) tertiary PDCs had pediatric endocrinologists. There was also a wide variation across PDCs in the number of patients followed, staff allocation, funding formulas, availability of team members and resources, provision of initial diabetes education, outreach and home services, as well as in psychosocial support to the patients.[21] I was unable to identify any research examining whether variability in the Ontario PDCs' supply of diabetes care providers reflects local and regional needs in pediatric diabetes health services and ensures equitable access to recommended diabetes care for children regardless of their residence.

1.3 Diabetes ketoacidosis (DKA): time trends, risk and protective factors

Recent updates on pediatric DKA trends are available from longitudinal projects: SEARCH for Diabetes in the US[22] and EURODIAB in Europe.[23] I was unable to locate current studies on pediatric DKA hospital admissions trends in Canada or Ontario from 2000 until present for either types of diabetes. According to the latest published data (2003), pediatric DKA hospital admission rates in Ontario remained stable at about 21/100 between 1991 and 1999.[24] Yet, the proportion of children presenting with DKA at diabetes diagnosis increased from 15% in

1994/95 to 22% in 1998/99.[24] The average annual DKA frequency in Ontario in 1994-2000 was 18.6%.[25] To compare, the frequency of DKA at diabetes diagnosis in the US was higher and remained stable in children and youth with T1D (n=5615) between 2002 and 2010: 30% in 2002-2003, 29% in 2004-2005 and 31% in 2008-2010.[22] A similar trend was observed in Europe. In Austria, the prevalence of DKA at diabetes diagnosis remained high in children and youth with T1D (n=4038) between 2005 and 2011: 38% in 2005-2009 and 37% in 2010-2011.[26,27] DKA at the onset of T2D diabetes is less common than in the case of T1D. In Canada, a study in Manitoba and Northwestern Ontario reported that 11% of all pediatric patients with T2D (n=120) experienced DKA episodes in 1986-1999.[28,29] In the US, DKA frequencies in youth with T2D (n=1425) were decreasing between 2002 and 2010: 12% in 2002-2003 and 6% in 2008-2010.[22]

The major cause of DKA at the onset of the disease is a delayed diagnosis.[7;12] Protective factors of DKA at T1D diagnosis include: having a first degree relative with T1D; parents with higher education; living in area with a higher background incidence of T1D; and being diagnosed at a hospital that has a diabetes team.[30] A systematic review of studies of DKA in children and young adults in 31 countries identified groups of children at an increased risk for DKA at the onset of diabetes: those younger than three years of age; from ethnic minority or migrant groups; without medical insurance (in the US); or with a lower body mass index.[12] One of the major causes of DKA in children with established diabetes is poor diabetes management, mostly related to insulin omission.[28,31] Recurrent DKA episodes are common for some individuals: 80% of all DKA episodes occurred among 20% of children in 2004-2009 in the US.[32] A UK study reported that 5% of patients accounted for 23% of all DKA episodes over a three-year period in 2005-2008.[33] Usually, DKA was associated with T1D diabetes; however, there is evidence that

children with T2D also develop DKA both at the onset and during the course of the disease.[22,29] Indigenous children with T2D in Northwestern Ontario and Manitoba were shown to be at risk of DKA at the time of diabetes diagnosis: all 13 of 120 (11%) children with T2D who experienced DKA were self-declared Indigenous.[29]

In children with established diabetes, risk of DKA increases in adolescent girls; children with psychiatric disorders; those with lower socio-economic status defined by income and educational level of parents, or those with longer duration of the disease. [34]An increased risk of DKA is also associated with the insufficient access to diabetes care. For example, in the US, un-insured children with diabetes were more likely to present with DKA than insured children, and their condition tended to be more severe and life threatening.[35] Canada, unlike the US, has a universal health care insurance; however, the Ontario population-based study showed that the DKA risk among children with T1D was significantly higher in those with lower income, [25] indicating that universal access to care may not eliminate income-based inequities in health outcomes for children with diabetes. There is evidence that comprehensive diabetes programs with education and telephone help have significantly reduced the DKA rates in children and adolescents.[36-38]

In Ontario, northern district health councils (DHCs) had age- and sex-adjusted pediatric DKA rates 2.3 times higher than in southern DHCs with the lowest DKA rates in 1991-1999.[24,39] This variation remained stable over the study period. It was similar to other pediatric conditions such as asthma and gastroenteritis, revealing a common pattern: that the more populated urban areas had lower rates of hospital admissions for acute complications compared to more remote and sparsely populated areas.[40,41] To what extent rural and remote residence contribute independently

to the risk of DKA for children with diabetes in northern parts of Ontario is not clear. European studies did not find significant differences in DKA frequency among children living in cities, towns, suburbs, or villages and rural areas in northern European countries such as Sweden, Lithuania, and Finland.[42,43] These findings cannot be extended to Canadian pediatric diabetic populations due to Canada's distinct geography (extremely vast territory) and population composition (higher proportion of immigrant population in larger cities and Indigenous peoples in northern regions). Moreover, research on adult populations in Ontario showed that individuals with diabetes in rural and remote or Indigenous communities were more likely to have acute diabetes complications.[44] It is important to note that close to 41% of Indigenous peoples in Ontario are under the age of 25 years[45] and that 26% of the population of Northern Ontario is children.[46,47] All of this supports a notion that it is imperative that we examine access to health care and outcomes for children in Northern Ontario.

1.4 Study rationale and research questions

My literature review indicated that the likelihood of DKA in children with diabetes is commonly associated with individual-level risk factors (e.g., age) or socio-economic factors (e.g., material deprivation). Less is known about system-level factors of DKA, associated with geography and rural residence in the Canadian context. Understanding of geographic/regional differences in health outcomes is important in highlighting systemic factors associated with inequity in health care access and quality.[48] Particularly, this is important in countries like Canada, where access to hospital and physician services is publicly insured and system-level barriers to diabetes care may not be as evident as in countries with private access to health care. The difference in pediatric DKA population rates between Ontario geographic regions may be a sign of that children in northern communities have a higher burden of diabetes and/or do not have access to the diabetes

care that they need.[49] In my literature review, I was unable to identify any research to date that has explored factors underlying this difference. Nor did I find studies that looked at pediatric DKA hospital admissions at the regional level. Since pediatric diabetes care in Ontario is managed at a regional (LHIN) level, this is an important gap in knowledge that must be addressed. Thus, **the first objective** of my study was to describe DKA prevalence rates in children with diabetes in Ontario by LHIN regions and compare Northern Ontario with other regions in Ontario.

I set two research questions for this objective:

1) What are trends in pediatric diabetes incidence in Ontario in 2004-2012? Is pediatric diabetes incidence higher in Northern Ontario compared with other Ontario regions?
2) What are trends in pediatric DKA prevalence rates in Ontario in 2004-2012? Are pediatric DKA prevalence rates higher in Northern Ontario compared with other Ontario LHIN regions?

Furthermore, my literature review indicated that the role of pediatric diabetes care in preventing DKA hospital admissions has not been fully assessed in the literature. Some studies showed that diabetes care by specialized multidisciplinary team led by a pediatrician was a protective factor against diabetes complications, including DKA; however, these findings were published between the late 1970s and 1990s and limited to several local medical centres.[36-38] To address this gap, **the second objective** of my study was to examine the relationship between DKA hospital admissions in Ontario children with established diabetes and their use of physician services for diabetes care.

Research questions related to this objective were:

3) What are patterns of use of physician diabetes care by Ontario children with diabetes? Are these patterns different in Northern Ontario compared with other Ontario regions?

4) For a child with established diabetes residing in Ontario, how the likelihood of DKA hospital admission is associated with the use of physician pediatric diabetes care? With Northern Ontario residence?

Table 1-1 shows how my research questions were addressed in three papers and presented in the manuscript.

Table 1-1: Manuscript structure

Research question	Paper	Manuscript
Research questions 1-3	Methods overview	Chapter 2
Research question 1	**Paper 1**: Incidence of pediatric diabetes in Ontario by LHIN	Chapter 3
Research question 2	**Paper 2**: DKA hospital admissions at diabetes diagnosis **Paper 3**: DKA hospital admissions in children with established diabetes	Chapters 4 and 5
Research question 3	**Paper 3**: Use of physician pediatric diabetes care by Ontario LHIN regions	Chapter 5
Research question 4	**Paper 3**: Effects of the use of physician diabetes care and geography on DKA hospital admission in children with established diabetes	Chapter 5

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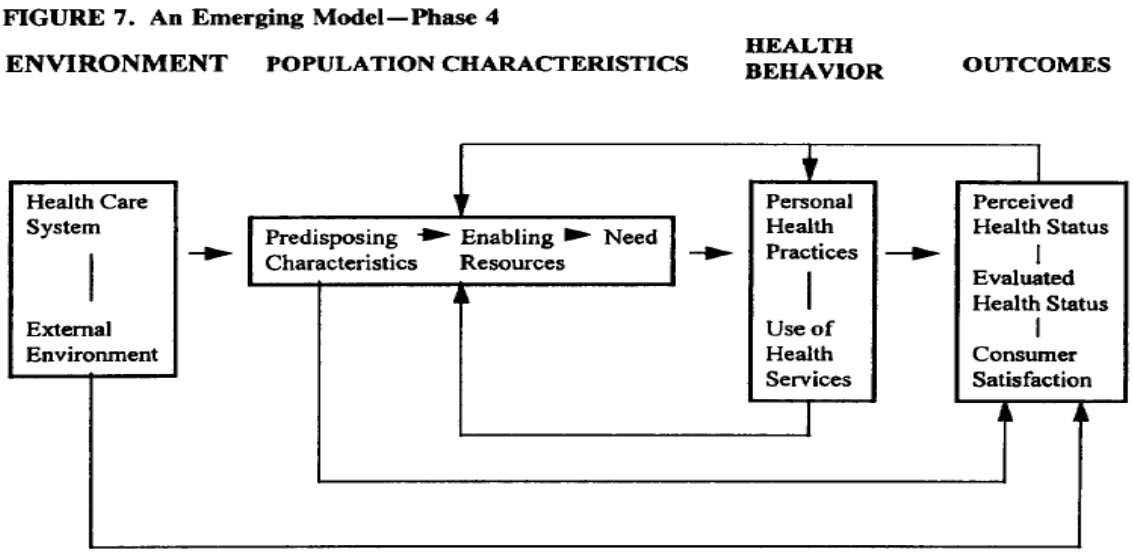
Chapter 2

Methods overview

In this chapter, I will introduce a conceptual model that guided my research and interpretation of findings, describe data sources, research design, and variables used in statistical analyses.

2.1 Conceptual model

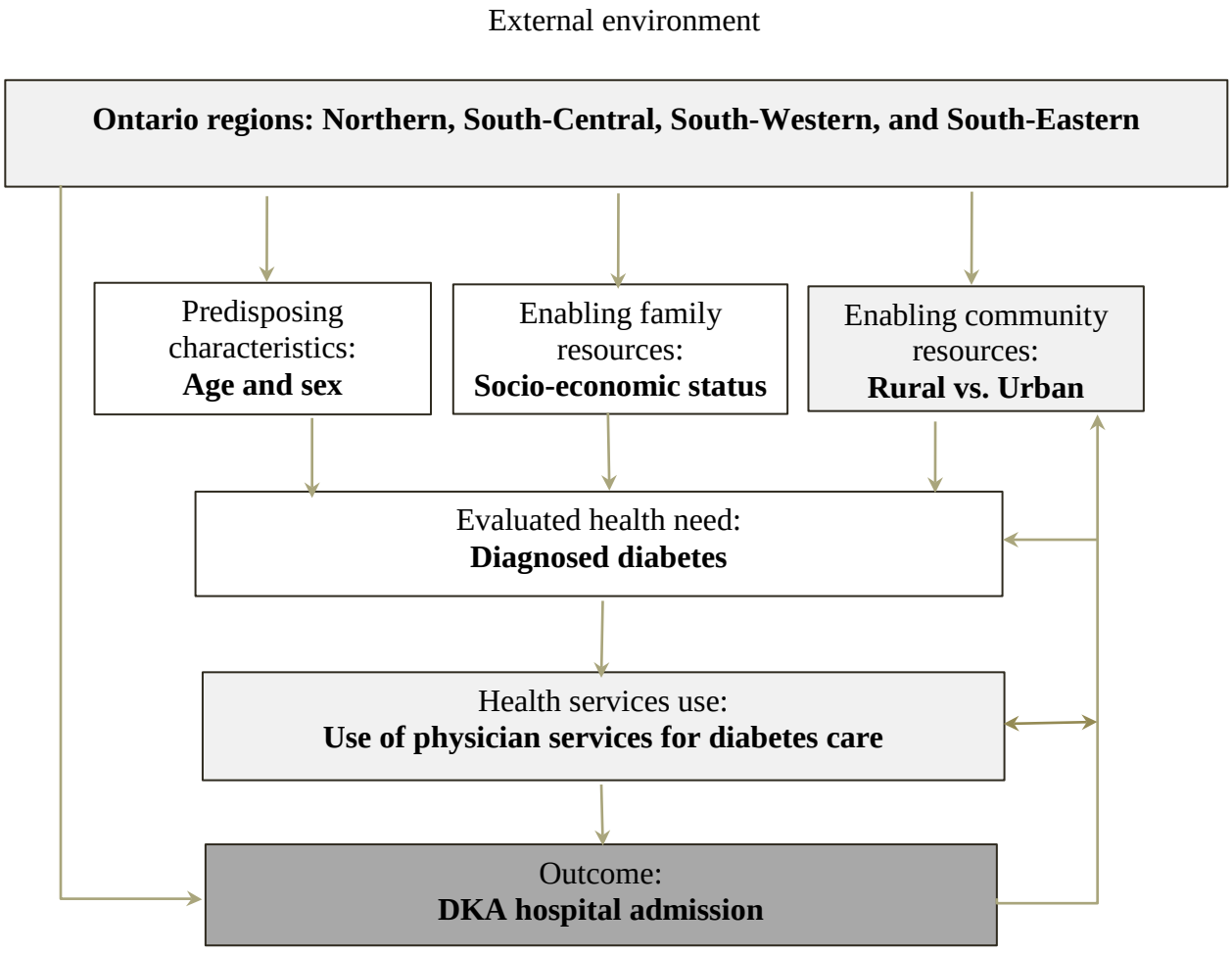
As described in the previous chapter, my research questions were concerned with examining the relationship between the use of physician services for pediatric diabetes care, geographic location (Northern Ontario versus Southern Ontario regions), and health outcomes (DKA hospital admission). The Andersen's model[1] has been used extensively to predict or explain utilization of health services[2] (Figure 2-1).



Source: page 8 in Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *Journal of Health and Social Behavior* 1996; 36(1):1:10 (see Appendix II for permission to reprint).

Figure 2-1: Andersen's model of health services use

The Andersen's model explains the use of health services by health needs which are shaped by the effects of system-wide and population characteristics, on one hand, and, on the other hand, the model accounts for the effect of the health services use on health outcomes. I applied Andersen's model to my research by defining four Ontario regions, i.e., Northern Ontario, South-Central, South-Western and South-Eastern, as *external contextual environment* of children's use of health services (Figure 2-2). Age and sex were seen as *predisposing* demographic characteristics. *Enabling family resources* were associated with family's socio-economic status.



Note: Shaded boxes indicate the study's variables of interest.

Figure 2-2: Conceptual model

Enabling community resources were defined by whether a child lives in a rural or urban community. An *evaluated health need* was defined as diagnosed diabetes. Health services were limited to physician's services for diabetes care. DKA hospital admissions were categorized as a proxy measure for *health outcomes*.

2.2 Data sources

My thesis research capitalized on the availability of provincial health administrative data on physician services and hospital admissions for children with diabetes in Ontario. These data were available through the Institute for Clinical and Evaluative Studies (IC/ES).[3] In health research, access to such data provides an opportunity to obtain a system-wide understanding of health services use patterns and health outcomes at population level that cannot be obtained using other sources of data (e.g., surveys). The secondary use of health administrative data for research purposes is also more economical compared with collection of primary research data.[4]

Access to the person-level linked data for my thesis was approved by the Laurentian University Research Ethics Board (file 6009778) and by the data privacy review at IC/ES. The IC/ES's Data Analytical Services (DAS) prepared datasets for my research. I accessed the data securely through the Data and Analytic Virtual Environment (IDAVE). All data analysis outputs were released from the IDAVE after the IC/ES DAS's confidentiality and privacy review.

Data sources. Three data sources were used in this study: the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System (CIHI-NACRS) and Ontario Health Insurance Plan (OHIP).[4]

The CIHI-DAD contains information abstracted from hospital records: each record in the database corresponds to a single hospital admission. In addition to information about diagnoses,

procedures, and type of physician providers, the CIHI-DAD includes mandatory data on patient demographic information, unique facility numbers and geographic location of patient residence and hospital location (e.g., county, municipality, LHIN, public health unit (PHU), postal code). The OHIP database contains all physician claims and shadow billings submitted to the provincial government for insured services provided to Ontario residents. Each OHIP database record represents a discrete service provided to a specific person, on a specific day. It includes mandatory information about the patient (encrypted health number, age, sex, geographic location, including municipality, postal code, FSA, census subdivision (CSD), statistical area classification (SAC), LHIN, PHU), the date that it occurred, the type of service provided, diagnostic information, the provider (geographic location, including county, municipality, postal code, FSA, LHIN, PHU, specialty), the associated fee code, and the total fee paid to the health care provider. The CIHI-NACRS contains records of all ambulatory visits in Canada for patients who were treated in day surgery, outpatient clinics and emergency departments (EDs).

2.3. Research design and variables

I employed a population-based longitudinal cohort design based on provincial administrative health data. The data included person-level health administrative data on DKA hospital admissions linked to the records of physician visits for diabetes care, including family physicians (FPs)/general practitioners (GPs), general pediatricians, pediatric and adult endocrinologists. The use of the population-based approach conferred external validity of results. The longitudinal design captured DKA hospital admissions along the course of the chronic disease at the individual level. The use of person-level linked data and accounting for both individual and contextual factors allowed avoiding the risk of ecological fallacy common to ecological studies.[5]

Study cohort. In this study, I defined children as individuals younger than 18 years old. The study population included all children who were newly diagnosed with diabetes and lived in Ontario from April 1, 2004 through March 31, 2015. All children in the cohort were followed during the course of diabetes until March 31, 2015 for a period of one to 11 years.

Case definition. Data for my study cohort was extracted at IC/ES from the Ontario Diabetes database (ODD), using a validated algorithm of pediatric diabetes case definition of at least four physician claims using a diabetes diagnostic code over a two-year (730-day) period.[6] This case definition has a specificity of about 99% and a sensitivity of up to 83% for Ontario children younger than 19 years (n=923).[6]

Time frames. I considered several criteria to decide about time frames specific to my study. Firstly, as DKA is a relatively rare event, to better capture DKA incidence time trends I needed as many years as possible. The most recent available data at the time of my data request was March 31, 2015. Secondly, to avoid inconsistencies in data coding, I decided to use only data, starting from 2002, when the new ICD-10-CA diagnosis coding was implemented and replaced the ICD-9 system in Ontario hospitals.[7] Finally, the new diabetes case identification algorithm required a two-year look-forward and two- year look-back period. Following these rationales, the study-specific dates were: (1) all children with new diabetes diagnosis between April 1, 2004 through March 31, 2013 (fiscal years 2004/05 to 2012/13) (accrual window) and (2) hospital admissions records were looked for DKA incidences and physician visits from the time of diabetes diagnosis through March 31, 2015 in OHIP, CIHI-DAD and CIHI-NACRS data (study

observation window)(Figure 2-3). These time frames provided 10-year of data available for follow-up (Table 2-1).

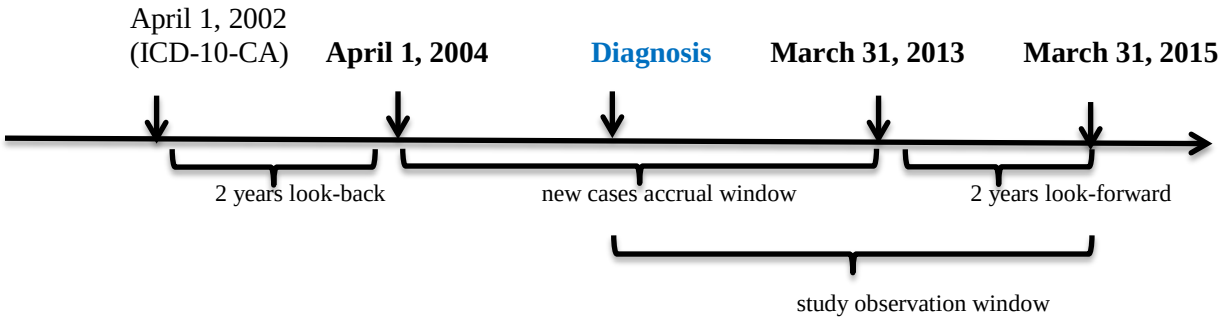


Figure 2-3: Study time frames

Variables for statistical analyses. A list of variables with definitions that were used in my statistical analyses is presented in Appendix III. DKA hospital admission was the main outcome variable identified in CIHI-DAD by ICD-10-CA codes (E10.0-10.12) for each child from the time of diagnosis through March 31, 2015. Health services use included all physician claims of services for each child, based on diagnosis and fee codes of the Ministry of Health Schedule of Benefits, Physician Services under the Health Insurance Act (October 1, 2013), recorded in the OHIP database, and all ED visits, recorded in CIHI-NACRS. Physician visits for diabetes care were identified by the OHIP diagnosis code 250 for diabetes or fee codes associated with diabetes management, e.g., “Diabetes management assessment by FP/GP” (K030), “Diabetes management by a specialist” (K045), “Diabetes team management” (K046). Duplicate or multiple claims for a patient on the same day to the same physician specialty were counted as one physician visit. For each physician visit in my dataset, a variable with the number of days since the date of diabetes diagnosis was available. For each ED visit, I requested information on

service date, main problem, triage level, ED visit indicator, and visit disposition status from the CIHI-NACRS database. I used the CIHI-NACRS element "disposition status", referring to the outcome of the ED visit (e.g., discharged at home, admitted, not seen or left, transferred), to avoid double count of the same event in both CIHI-DAD and CIHI-NACRS and count only those ED encounters that had "discharged at home" as a disposition status. Charlson index was used to identify comorbidity at the time of diagnosis. Common comorbidities in children with diabetes include thyroid disease, celiac disease, cardiovascular and mental disorders (anxiety and depression), microvascular diseases (neuropathy, nephropathy and retinopathy).[8]

Variables of child's geographic LHIN region and rurality were derived from postal codes of the child's residence recorded in RPDB (at diabetes diagnosis) and in OHIP claims (in the follow-up period) based on Statistics Canada Statistical Area Classification (SAC) codes.[9] A proxy measure of socio-economic status (SES) such as the Ontario Marginalization Index (ON-Marg) suited my research purposes as it has been shown to be associated with health outcomes and it is stable across time periods and different geographic areas (for example, cities and rural areas).[10] I used the ON-Marg's material deprivation dimension that is computed based on the proportions of the population without a high school diploma, lone parents, those on government transfer payments, unemployed, low-income and living in dwelling in need of major repair, The ON-Marg quintile scores are available for the varying geographic units. For my thesis, I used ON-Marg quintile scores at the level of census subdivisions.

In my data, each child had two identifiers: a unique ID and the cohort number (one to nine). Person-level factors included date of the diabetes diagnosis, age group at diagnosis, and sex.

All children were followed from the time of their diabetes diagnosis through March 31, 2015 for a minimum of two and maximum of eleven years, or until the age of 18. Data was analyzed using a unique person (research question 1-3) and a person-year (research question 4) as units of analyses (Table 2-1). Thus, each annual record for each person in the cohort represented one person-year. The use of person-years is well suited for accounting for the varying number of years available for each person and calendar year in the cohort design.[11] This approach enabled me to maximize the use of datasets including as many records as possible to the statistical analyses.

Table 2-1: Data structure by unique persons and person-years

Cohort	Follow-up year [a)]											Person-years
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	
1	D	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	**PY1**
2		D	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	**PY2**
3			D	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	**PY3**
4				D	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	**PY4**
5					D	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	**PY5**
6						D	Year 1	Year 2	Year 3	Year 4	Year 5	**PY6**
7							D	Year 1	Year 2	Year 3	Year 4	**PY7**
8								D	Year 1	Year 2	Year 3	**PY8**
9									D	Year 1	Year 2	**PY9**
	N_{2004}	**N_{2005}**	**N_{2006}**	**N_{2007}**	**N_{2008}**	**N_{2009}**	**N_{2010}**	**N_{2011}**	**N_{2012}**			**Total PYs**

Notes: "D" = year of diagnosis, N_{year} = number of children newly diagnosed with diabetes.
[a)] Data were obtained for fiscal years. For example, "2004" year covers the period from April 1 2004 to March 31 2005.

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Chapter 3

Paper 1. Recent trends in the diabetes incidence in children (0-18 years) in Ontario, Canada: estimates from the provincial diabetes database based on health administrative data

Oxana Mian, Elizabeth Wenghofer, Nancy Young and Liisa Jaakkimainen

For submission to Pediatric Diabetes

Abstract

Purpose: To estimate the incidence of diabetes (type 1 and type 2 combined) in children and youth aged 0-18 years in Ontario, Canada, between 2004 and 2012.

Method: Data on children (0-18 years) who resided in Ontario and were diagnosed with diabetes from April 1, 2004 through March 31, 2012 was obtained from a provincial diabetes registry. Incidence rates (IRs) were calculated by age group (0-6, 7-12, and 13-18 years) and sex for the entire province and geographic regions of South -Western, South-Central, South-Eastern and Northern Ontario. IRs for geographic regions were standardized to the Ontario population of children (0-18 years) using a direct method. Poisson distribution of new diabetes cases was assumed. Confidence intervals (95% CI) were computed using an exact Poisson method. Poisson regression models were used to estimate annual percent change (APC) of diabetes IRs and assess significance of year, age group, sex and region in predicting incidence of diabetes in the study population.

Results: From 2004 to 2012, a total of 10,617 cases of new diabetes diagnoses were identified in Ontario children. The crude IR varied from 33.3 (95% CI 31.2-35.4) per 100,000 children in 2004 to 43.8 (95% CI 41.4-46.3) per 100,000 children in 2012. Youth (13-18 years) had the highest IR among other age groups, reaching 55.0 (95% CI 48.2-61.4) per 100,000 children in 2012. Two distinct patterns related to the diabetes incidence were observed: a rapid increase in IR between 2004 and 2008 (APC of 6.0%, $p<0.0001$) and stabilization in IR between 2009 and 2012 (APC of 1.0%, $p=0.99$). There was a significant north-south difference in diabetes incidence (rate ratio of 1.22, $p<0.0001$) with the highest age-and-sex standardized IR of 46.4

(95% CI 44.5-48.0) per 100,000 children/year in Northern Ontario compared to the lowest 38.0 (95% CI 36.3-39.4) per 100,000 children/year in South-Central Ontario. Poisson model-adjusted IRs were associated with age group (df=2, Chi-sq=374, $p<0.0001$), year of diagnosis (df=8, Chi-sq=115, $p<0.0001$), and region (df=3, Chi-sq=59, $p<0.0001$) and were not associated with sex (df=1, Chi-sq=0.25, $p=0.62$), indicating similar to the observed time trends and relationships within the parameters.

Conclusions: Pediatric diabetes incidence in Ontario is among the highest in the world; however, the steady increase in diabetes incidence in 2004-2008 plateaued in 2009-2012. Within the province, youth (13-18 years) and children residing in Northern Ontario were at the highest risk of diabetes.

Introduction

Over the past few decades, the incidence of diabetes (both type 1 and type 2) has been steadily increasing in children and youth worldwide by an average of 5.3% in North America, with some variation internationally (4.0% in Asia and 3.2% in Europe).[1-4] The highest incidence of type 1 diabetes (T1D) (also referred as "insulin-dependent diabetes mellitus") has been observed in northern European countries (with the highest incidence in Finland – 64 per 100,000 children 0-14 years/year).[5] Recent evidence from Sweden,[6] Finland,[7] Norway,[8] Netherlands, and Czech Republic [9] indicated a possible levelling off of the escalation of T1D incidence for children and youth in recent years after a rapid increase in 1989-2000. There was also a shift of more rapid increase of T1D incidence from younger (0-5 years old) to the older age groups in more recent years. Type 2 diabetes (T2D) is the most common form of diabetes, with more than 90% of all Canadian people with diabetes having T2D.[10] It has historically been viewed as an adult disease, yet has been also on the rise in children and youth for the last two decades.[2,3,11,12] A worldwide trend indicates the highest incidence of T2D is among Indigenous children in North America (300 per 100,000 children aged 0-14 years among Pima Indians in the USA) and the lowest incidence in children in European countries (0.83 per 100,000 in the UK, 0 per 100,000 in Netherlands).[4]

Canada is among the 10 top countries in the world in terms of diabetes incidence in children and youth.[1,4] The latest Canadian national data indicated 25,693 cases of all types of pediatric diabetes (a prevalence rate of 0.3%) and 3,287 new cases of diabetes (incidence of 40 per 100,000 children) among Canadians younger than 19 years in 2008/09.[13] A national estimate specific to T1D incidence is not available in Canada; however, it was estimated that about 90% of Canadian children with diabetes have T1D.[14] A national population-based surveillance study

indicates that the observed minimum incidence of physician-diagnosed T2D in Canadian children (0-18 years) in 2006-2008 was 1.54 per 100,000 children/year in general population. The incidence rate of T2D in children varied across Caucasian, Indigenous (not including on-reserve populations), Asian and African/Caribbean ethnicities: 0.54, 23.2, 7.7 and 1.9 cases per 100,000 children/year respectively.[11] In Canada, 8% of children diagnosed with T2D were younger than 10 years of age compared to 3.6% in the U.S.[2,12]

Within Canada, six of 14 Canadian provinces, including Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Ontario and Quebec have reported estimates of diabetes incidence in children and youth (see a summary of published studies in Appendix IV). The reported incidence rates (IRs) vary in terms of time period, age range and diabetes type covered.[11,14-27] Newfoundland and Labrador reported the world's highest incidence of T1D in children (50 per 100,000 children/year) in 2007-2010.[20-22] In Quebec, T1D incidence was 15 per 100,000 children (0-18 years)/year in 1989-2000.[19] In Alberta, in 2007, the incidence of diabetes (both types) in non-Aboriginal children and youth (0-20 years) was 49 per 100,000 and 59 per 100,000 in Aboriginal children in the same age group. [23] In British Columbia, T1D incidence rate was 26 per 100,000 children (0-19 years) and T2D incidence rate was 5.5 per 100,000 children (0-19 years) in 2007. Manitoba reported T2D incidence comparable to the incidence of T1D: 21 per 100,000 in children (0-18 years) in Winnipeg, in 2011.

Ontario is the most populous Canadian province: almost 40% of 7.9 million Canadian children and youth aged 0-18years resided in Ontario (3.04 million) in 2016.[28] The most recently reported diabetes incidence in Ontario children (0-19 years) was 32.3 per 100,000 children in 2003, with

an annual percent change (APC) of 3.1% from 1994 to 2003 for both diabetes types combined.[18] Population-based estimates of diabetes in children are important for surveillance and health resources planning. Data on long-term trends of the diabetes incidence may also contribute to the understanding of the etiology of diabetes in children and youth. However, there is a gap of 15 years in estimates of diabetes incidence in Ontario children that have not been updated since 2003.[18] The purpose of our study was to address this gap and update the diabetes incidence in Ontario children from 2004 to 2012, using a provincial population-based diabetes registry based on health administrative data. The second aim was to examine differences of diabetes incidence between age and sex groups, between Ontario regions and over time. This level of detail has not been described previously for this population and is important to inform health planning.

Methods

A population-based retrospective cohort design was used to estimate diabetes IRs based on data from the Ontario provincial diabetes registry. These data were accessed through Data and Analytical Services (DAS) at the Institute for Clinical Evaluative Sciences (IC/ES), using a secure virtual desktop infrastructure (VDI). Statistical analysis was performed using SAS software, v.9.3 of the SAS System for Windows (©2011 SAS Institute Inc., Cary, NC, USA). The Research Ethics Board of Laurentian University approved this study (file 6009778).

The study population inclusion criteria were a) Ontario residency, b) age of 18 years old or younger, and c) a new diagnosis of diabetes in the period from April 1, 2004 through March 31, 2012. These cases were identified at IC/ES in the Ontario Diabetes Database (ODD), a provincial registry based on health administrative data that is systematically collected in the provincial

universal health care system. The age range (0-18) was chosen in line with a provincial definition of children for pediatric health services eligibility. New pediatric diabetes cases in the ODD were identified using a case definition algorithm that requires four physician claims with diabetes code 250 over a two-year period.[18] The algorithm has a specificity of 99% and a sensitivity of 83% and was previously validated for Ontario children (0-19 years, n=923).[18] The available health administrative data on physician claims does not distinguish between diabetes types. Therefore, our analysis was performed for all diabetes types combined.

Data on year of diabetes diagnosis, age group at diagnosis (0-6, 7-12, 13-18 years of age), sex, and a geographic region of residence (South-Western, South-Central, South-Eastern and Northern Ontario) was available for each child in the study population. Boundaries for geographic regions were set based on 14 Ontario Local Health Integration Networks (LHINs), which represent health authorities, responsible for regional administration of public health services in the province.[29] LHINs were merged into four groups for this analysis: South-Western Ontario included Erie St. Clair, South West, Waterloo Wellington, and Hamilton Niagara Haldimand Brant LHINs; South-Central Ontario included Central West, Toronto Central, Central, and Central East LHINs; South-Eastern Ontario included South East and Champlain LHINs; and Northern Ontario included North East and North West LHINs.

The Poisson distribution of new diabetes diagnosis counts was assumed suggesting that diabetes occurs independently in different children and the likelihood that a new diabetes case will occur in a short period is proportional to the number of people or period of time.[30] We calculated observed crude, age, sex, and age-and-sex specific incidence rates (IRs) for the entire province

and age-and-sex-standardized diabetes IRs for each region. Crude IRs were calculated for each year with a number of new cases of diabetes diagnosis as a numerator and the total number of children population in Ontario as a denominator. Age-specific, sex-specific, and age-and-sex-specific diabetes IRs were calculated for each year with the number of new cases of diabetes in each age, sex, age-and-sex group divided, respectively, by the total number of children in the age, sex or age-and-sex group. Confidence intervals (95%) for observed IRs were calculated using a Poisson exact method. IRs for geographic regions were standardized to Ontario population of children (0-18 years) by age and sex groups using the direct method. Confidence intervals (95%) and APC of regional IRs were estimated using Poisson regression model with year and region as independent predictors. A Poisson regression model of age-and-sex specific diabetes IR (dependent variable) adjusted for year, age group, sex and geographic region (independent predictors) was computed to assess a significance of each predictor of diabetes incidence in the study cohort. The model was offset with the natural logarithm of the number of children in each age-and-sex group. Graphs of age-and-sex-specific IRs over the nine-year period and Poisson model-adjusted IRs (least squared means with 95% CIs) by year, age group, sex and geographic region were produced using SAS software. All of the tests were two-sided and a p-value of less than 0.05 was considered statistically significant. Bonferroni correction of critical p value was used in case of multiple comparisons.

Results

There were 10,617 newly diagnosed cases of diabetes in Ontario children aged 0 to 18 years from 2004 to 2012. Thus, the crude IR was 40.2 per 100,000 (95% CI 36.3-44.6) children/year over the nine-year period. The diabetes IR varied over time from 33.3 per 100,000 children in 2004 to 43.8 per 100,000 children in 2012 (Table 3-1).

Table 3-1: Observed diabetes incidence per 100,000 children, by year and year periods

Year[a]/ period	New diabetes cases, number	Ontario children 0-18 years, number	Crude incidence rate (95% CI), per 100,000 children/year	
2004	984	2,959,006	33.3	31.2-35.4
2005	1020	2,955,802	34.5	32.4-36.7
2006	1159	2,953,573	39.2	37.0-41.6
2007	1204	2,945,089	40.9	38.6-43.3
2008	1207	2,939,302	41.1	38.8-43.4
2009	1281	2,928,564	43.7	41.4-46.2
2010	1250	2,922,900	42.8	40.4-45.2
2011	1241	2,916,208	42.6	40.2-45.0
2012	1271	2,900,551	43.8	41.4-46.3
2004-2012	10617	26,420,995	40.2	36.3-44.6
2006-2008	5574	14,752,772	37.8	34.7-41.2
2009-2012	5043	11,668,223	43.2	37.2-50.2

Notes: [a] Fiscal years used for collection of health administrative data in Ontario last from April 1st to March 31st: e.g., 2004=April 1, 2004 to March 31, 2005.

Age and sex differences in diabetes incidence. Diabetes incidence increased with age: youth (13-18 years), n=4455 had the highest IR of 47.9 per 100,000/year and the youngest children (0-6 years), n=2472 had the lowest IR (27.8 per 100,000/year) (Table 3-2). The sex-specific IRs were not different for girls (39.5 per 100,000/year), n=5087 and boys (40.9 per 100,000), n=5530; however, there were sex differences in the youngest (0-6 years) and oldest (13-18 years) age groups with higher IRs among boys than girls (Table 3-2).

Changes in diabetes IRs over time. The observed APC of diabetes incidence was 3.2% over the 2004-2012 period (Table 3-2). There were two time periods with distinct APCs: 2004-2008 with an APC of 6.0% (95% CI 3.6-8.5, $p<0.0001$) and 2009-2012 with an APC of 1.0% (95% CI 0.98-1.06, $p=0.99$). Youth (13-18 years) had the largest increase of incidence in the entire studied period (APC of 4.1%, $p<0.001$) compared to other age groups. The youngest children (0-6 years) had the lowest APC of 2.2% ($p<0.05$). The overall APCs were not different for girls (3%) and boys (3.4%) in the entire studied period. However, in 2004-2008, diabetes incidence grew faster in boys than in girls (APC of 8.5% and 3.4%) and in 2009-2012 it was declining in boys while still growing in girls (APC of -1.1% and 1.3%)(Table 3-2).

Table 3-2: Diabetes incidence rates and annual percent change by age group and sex[a]

	Incidence rate, per 100,000 children/year			Annual percent change, %		
	2004-2012	2004-2008	2009-2012	2004-2012	2004-2008	2009-2012
All cases (n=10,617)	40.2	37.8	43.2	3.2***	6.0***	1.0
0-6 years (n=2472)	27.8	27.0	28.9	2.2*	6.6***	0.0
7-12 years (n=3690)	44.9	42.2	48.3	3.2***	6.0*	-1.1
13-18 years (n=4455)	47.9	44.0	52.8	4.1***	5.7***	1.3***
Girls (n=5087)	39.5	37.1	42.6	3.0***	3.4	1.3
Boys (n=5530)	40.9	38.5	43.9	3.4**	8.5***	-1.1
0-6 years						
Girls (n=1143)	26.4	25.6	27.4	1.5	2.8	-0.3
Boys (n=1329)	29.2	28.3	30.3	2.7*	10.0****	0.2
7-12 years						
Girls (n=1818)	45.4	43.2	48.1	2.8****	4.6*	2.0Ł
Boys (n=1872)	44.5	41.2	48.6	3.6**	7.5*	-4.0****
13-18 years						
Girls (n=2126)	46.8	42.2	52.6	4.4****	2.8	2.0‡
Boys (n=2329)	48.9	45.7	53.0	3.9****	8.4****	0.7

Notes: [a] See Appendix V for 95% confidence intervals.

P-values for annual percent change within the time period: ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05. Ł p=0.32. ‡ p=0.09

When age-and-sex specific groups were compared, boys in the youngest (0-6 years) and the oldest (13-18 years) age groups had the highest increase of diabetes incidence in 2004-2008 with a stable IR in 2009-2012. There was a significant decrease of diabetes incidence in boys (7-12 years) in 2009-2012 (-4%). Overall, in 2009-2012 the diabetes incidence continued increasing only in girls (7-18 years), but the APC (2%) for this group was not statistically significant (Table 3-2, see also Appendix VI).

Regional differences in diabetes incidence. Diabetes IRs varied across Ontario regions (Table 3.3). In 2004-2012, Northern Ontario had the highest IR of 46 per 100,000 and South-Central Ontario had the lowest IR of 38 per 100,000. The APC also varied across Ontario regions. Thus, in 2004-2012, South-Central Ontario had the largest APC of 4.1%, South-Western Ontario showed a lower APC (2.9%), while Northern and South-Eastern Ontario had non-significant APCs (1.6% and 1.9%, respectively). The difference in diabetes incidence between Northern Ontario and other regions decreased almost two times due to a more rapid growth of diabetes incidence in South-Central and South-Western regions compared to Northern Ontario.

Table 3-4 shows between-region rate ratios of diabetes incidence in children across Ontario regions. The largest difference in diabetes incidence was observed between South-Central and Northern Ontario (rate ratio of 1.22, 95% CI 1.15-1.29) and the smallest one between South-Western and South-Eastern Ontario (1.04, 95% CI 0.88-1.1). The rate ratios decreased from the period of 2004-2008 to 2009-2012 so that the only statistically significant difference at the p=0.05 level (p=0.05/6=0.008, considering Bonferroni correction for 6 comparisons,) was observed between Northern and South-Central Ontario (rate ratio=1.14, 95% CI 1.05-1.23).

Table 3-3: Age-and-sex standardized diabetes incidence rates and annual percent change by Ontario region and year

	Incidence rate, per 100,000 children/year			Annual percent change, %		
	2004-2012	2004-2008	2009-2012	2004-2012	2004-2008	2009-2012
Ontario (n=10,617)	41.9	37.8	43.2	2.6****	6.0****	0.0
South-Central (n=5236)	38.0	34.9	41.9	4.1****	6.5****	0.0
South-Eastern (n=1387)	41.1	39.8	42.7	1.9	4.9	-1.3
South-Western (n=3247)	42.6	40.6	45.2	2.9***	5.9****	1.1
Northern (n=747)	46.4	45.4	47.5	1.6	6.6*	-2.4

Notes: See Appendix VI for 95% confidence intervals.

P-values for annual percent change within the time period: ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05.

Table 3-4: Between-region rate ratios of age-and-sex standardized diabetes incidence by time period, 95% confidence intervals

Ontario regions	2004-2012	2004-2008	2009-2012
South-Eastern versus South-Central	1.08* (1.02-1.14)	1.14**** (1.07-1.22)	1.02 (0.94-1.11)
South-Western versus South-Central	1.12**** (1.06-1.18)	1.16**** (1.09-1.24)	1.08 (0.99-1.17)
Northern versus South-Central	1.22**** (1.15-1.29)	1.30**** (1.22-1.39)	1.14* (1.05-1.23)
Northern versus South-Western	1.09* (1.03-1.14)	1.12** (1.05-1.19)	1.05 (0.97-1.14)
Northern versus South-Eastern	1.13**** (1.07-1.19)	1.14**** (1.07-1.21)	1.11 (1.03-1.21)
South-Western versus South-Eastern	1.04 (0.98-1.10)	1.02 (0.96-1.09)	1.06 (0.98-1.15)

Notes: [a] If Bonferroni correction is applied for 6 comparisons, for p=0.05 level, each comparison should be tested at the level of 0.05/6=0.008 (similarly, for p-level 0.01 adjusted p=0.01/6=0.0017, for p-level 0.001 adjusted p=0.001/6=0.00017, and for 0.0001 level, p= 0.0001/6=0.000017).

****p<0.0001, ***p<0.001, **p<0.01, *p<0.05 (considering Bonferroni correction within each time period).

Diabetes incidence rates adjusted for year, age group, sex and region. A Poisson regression model was used to estimate diabetes IRs, adjusted for year, age group at diagnosis, sex and region (model's goodness of fit value=154.6, df=184, value/df=0.84)(Table 3-5). Model-adjusted diabetes IRs were significantly associated with age group (df=2, Chi-sq=374, p<0.0001), year (df=8, Chi-sq=115, p<0.0001), and region (df=3, Chi-sq=59, p<0.0001) and were not associated

Table 3-5: Diabetes incidence rates by year, age group, sex and Ontario region, per 100,000 children/year (Poisson model adjusted estimates)

Parameter	Least Squared Mean (95% CI)	Parameter Estimates		
		Exp (estimate) (Wald 95% CI)	Wald Chi-Square	P-value
Intercept	33.2 (26.8-41.0)		1040.35	<0.0001
Year				
2004	33.5 (31.5-35.5)	0.75 (0.70-0.81)	54.1	<0.0001
2005	34.7 (32.8-36.8)	0.78 (0.72-0.84)	41.9	<0.0001
2006	39.5 (37.4-41.8)	0.89 (0.82-0.95)	10.3	0.001
2007	41.2 (39.0-43.5)	0.92 (0.86-0.99)	4.5	0.03
2008	41.5 (39.3-43.8)	0.93 (0.87-1.00)	3.9	0.05
2009	44.3 (42.0-46.7)	0.99 (0.92-1.07)	0.04	0.84
2010	43.4 (41.1-45.7)	0.97 (0.91-1.04)	0.6	0.45
2011	43.2 (41.0-45.6)	0.97 (0.9-1.04)	0.7	0.40
2012	44.6 (42.3-47.0)	1	-	Reference
Age at diagnosis				
13-18 years old	49.0 (47.3-50.7)	2.11(1.65-2.69)	35.1	<0.0001
7-12 years old	46.9 (45.1-48.7)	1.90 (1.47-2.46)	23.7	<0.0001
0-6 years old	28.9 (27.5-30.3)	1	-	Reference
Sex				
Girls	40.8 (39.4-42.2)	0.89 (0.66-1.20)	0.6	0.45
Boys	40.3 (38.9-41.7)	1	-	Reference
Ontario region				
Northern	44.0 (41.0-47.2)	1.31 (1.05-1.64)	5.8	0.02
South-Western	40.4 (38.4-42.4)	1.33 (1.13-1.56)	18.4	<0.0001
South-Eastern	41.7 (40.3-43.0)	1.31 (1.16-1.47)	12.3	0.0005
South-Central	36.3 (35.3-37.2)	1	-	Reference

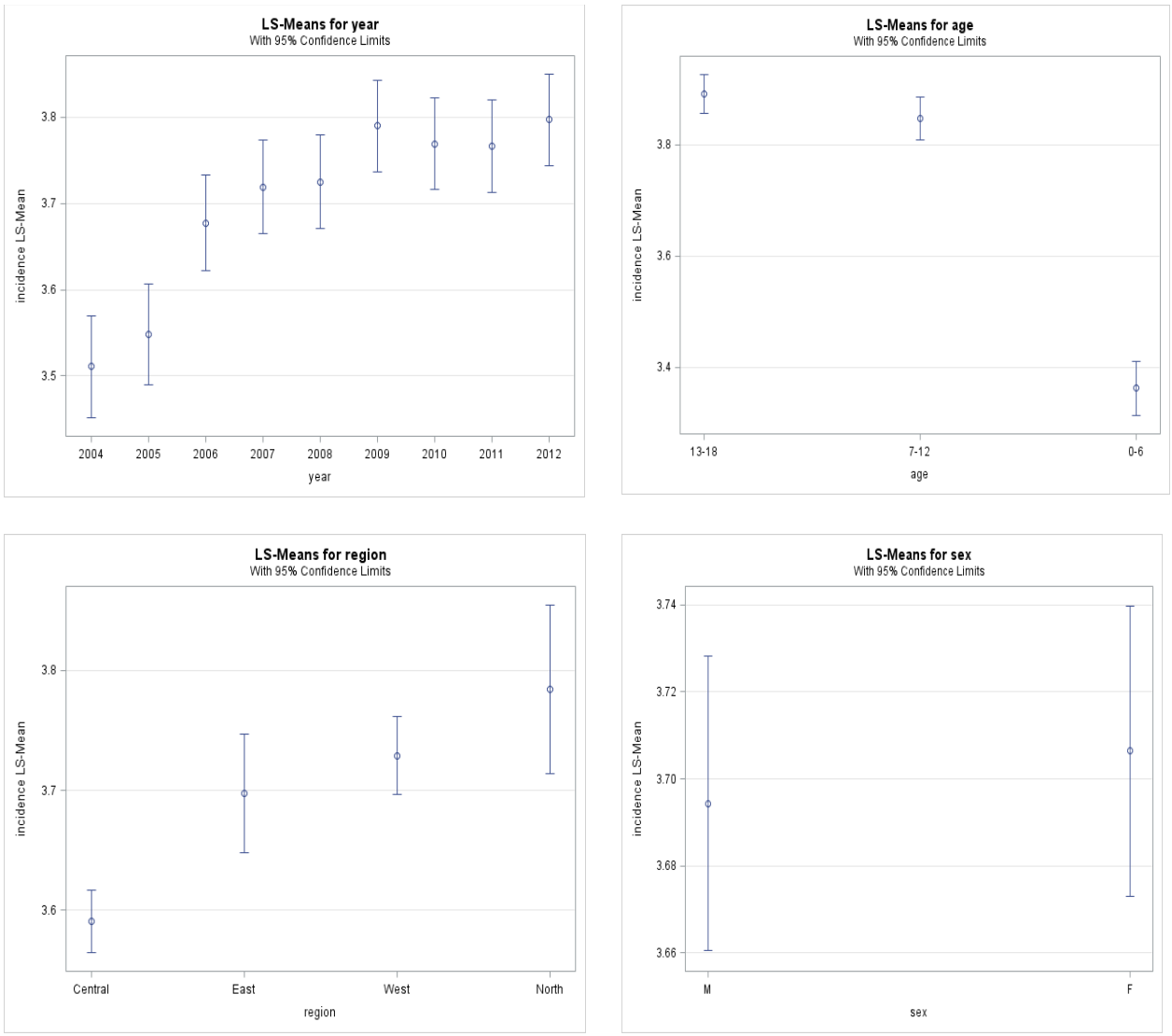

Figure 3-1: Diabetes incidence rates by year, age group at diagnosis, sex and geographic region (Poisson model-adjusted least squared (LS)-means with 95% confidence intervals)

with sex (df=1, Chi-sq=0.25, p=0.62). Similar to the observed IRs, Poisson model-adjusted IRs indicated two periods with distinct IRs: 2004-2008 and 2009-2012 (Figure 3-1).

Poisson model-adjusted IRs were higher in the older age groups (49.0 per 100,000/year for 13-18 years old and 46.9 per 100,000/year for 7-12 years) than in the younger children (28.9 per 100,000/year for 0-6 years old)($p<0.0001$)(Figure 3-1). Rate ratios of model-adjusted IRs showed that diabetes incidence for older children was almost two times higher than for the youngest (0-6 years) children: rate ratio of 1.7 (95% CI, 1.60 -1.80) between 13-18 years-old group and 0-6 years-old group and 1.6 (95% CI, 1.53-1.73) between the 7-12 year- olds and 0-6 year-olds. A difference in diabetes incidence between 13-18 year-olds and 7-12 year-olds was not statistically significant (1.05, 95% CI 0.99-1.10, p=0.10)(not shown in Table 3-5).

Discussion

Our study showed that the crude diabetes IR for T1D and T2D combined was 44.0 per 100,000 Ontario children (0-18 years) in 2012. This is almost 80% greater than the rate of 25.0 per 100,000 children reported in the province in 1994.[18] Our results indicate that the diabetes incidence in Ontario children tends to be lower than in other Canadian provinces, including Newfoundland and Labrador and Alberta, and higher than in British Columbia and Quebec (Appendix IV). Thus, in Newfoundland and Labrador the IR of 50.0 per 100,000 children (0-14 years)/year was reported for T1D in 2007-2010.[22] In Alberta, the latest published IR was 49 per 100,000 children for the 0-14 age group for both diabetes types in 2007 that is higher than the IR of 40 per 100,000 for Ontario children aged 0-18 years in the same year.[23] British Columbia reported the IR of 31.5 per 100,000 children in 2007 for both diabetes types (similar to our study) for children aged 0-19 years. This IR included 26.0 per 100,000 children for T1D and 5.5

per 100,000 children for T2D.[14] The latest reported IR for Quebec children was 15.0 per 100,000 children (0-18 years of age) in 2000 for T1D only.[19]

Considering that the age range of our study cohort (0-18) was wider than in the most studies in European countries (0-14 years), our study results indicated that Ontario has a risk of pediatric diabetes that may be comparable with some Scandinavian countries (Sweden, Norway) and greater than was reported for other European countries, the US and Australia. Diabetes incidence in Ontario children was lower than in Finland, a country with the highest incidence of T1D in the world (64.0 per 100,000 children younger than 15 years in 2011).[7] In Sweden, the diabetes IR was 44.0 per 100,000 children (0-14 years)/year in 2005-2007[6] and in Norway, the diabetes IR was 33.0 per 100,000 children (0-14 years)/year in 2004-2012.[8] Other European countries reported lower T1D incidence in children: 21.0 per 100,000 children (younger than 15 years)/year in Spain in 2008-2012; [31] 25.0 per 100,000 children (younger than 18 years)/year in the Italian region of Apulia in 2009-2013;[32] and, 23.0 per 100,000 children (0-14 years)/year in Germany in 2004-2008.[33] Netherlands reported diabetes incidence of 25.2/100,000 children (younger than 19 years)/year in 1998-2011[34] and 21.4/100,000 children younger than 14 years in 2011.[35] In Australia, the T1D incidence was 23.2 per 100,000 children (0-14 years)/year in 2000-2011.[36] In the US, the most recent study reported T1D IR of 22.0 per 100,000 children (0-19 years of age)/ year and the T2D incidence rate of 13.0 per 100,000 youths (10-19 years)/year in 2002-2012.[2] This is about 35.0 per 100,000 for both types combined that is lower than we found for Ontario children (for a one-year narrower age range) in 2004-2012.

Age and sex differences. We showed that Ontario youth (13-18 years) had the highest diabetes incidence increase of 4% per year over the studied period compared with other age groups. In 2012, the diabetes IR for this group reached 55.0 per 100,000 children in youth girls and 53.0 per 100,000 children in youth boys. This is in line with findings from population-based studies from other countries.[8,36-43] Youngest (0-6 years) boys in Ontario had a higher incidence of diabetes than girls (0-6 years) that was similar to other Canadian regions (Newfoundland and Labrador) and other countries. This sex difference is often found in populations with a high incidence of T1D.[44] The 10% increase of diabetes incidence in younger Ontario boys (0-6 years) in our study exceeds previously reported annual increase in this group in other countries.

North-south difference in diabetes incidence. We found there was a significant north–south difference in diabetes incidence in Ontario children. Northern Ontario had the highest age-and-sex standardized diabetes incidence over the studied period (46.4 per 100,000) and South-Central Ontario had the lowest age-and-sex standardized diabetes incidence (38.0 per 100,000). With a significant increase of diabetes incidence in South-Central Ontario (APC of 4%) and a non-significant increase of diabetes incidence in Northern Ontario (APC of less than 2%), the north–south difference has decreased from 2004-2008 (rate ratio of 1.3) to 2009-2012 (rate ratio of 1.15). The difference in diabetes incidence between children in South-Eastern and South-Western Ontario was not significant. This is in line with previous Ontario results that reported the lowest diabetes incidence in children in the Toronto Metropolitan Area (a large part of South-Central Ontario in our study) and one of the highest diabetes incidence in Northwestern Ontario (part of Northern Ontario).[26]

The north-south difference in diabetes incidence in Ontario children that we found in our study was also observed in Europe where a higher incidence was reported in northern Europe (Scandinavian countries) than in southern Europe (Spain and Italy). Higher incidence of diabetes in Northern Ontario children than in other Ontario regions may be explained by various factors. For T1D it is suggested that children in northern regions may be more at risk of diabetes due to the northern latitude and deficiency in vitamin D.[45] Other factors may include lower rates of breastfeeding in Northern Ontario,[46] infant formula and cow's milk introduction, known to be associated with a higher diabetes incidence in childhood.[47] Northern Ontario has a higher proportion of Indigenous populations that are at a higher risk of T2D[48] that may contribute to the higher IR of diabetes in Northern Ontario children. A higher increase of diabetes incidence in South-Central Ontario may be due to a higher proportion of immigration populations who are also at a higher risk of T2D.[11,12] Overall, similar to other studies, our analysis showed that diabetes incidence in Ontario children was independently associated with age group, year and region and was not associated with sex.

Time trends. Our study findings indicated that diabetes incidence in Ontario children has been increasing, on average, at 3.2% per year between 2004 and 2012. This is similar to previously reported APC of 3.1% in Ontario children in 1994-2003[18] and close to the diabetes incidence rate increase reported for T1D in other countries (for example, 3.6% per year until 2005 in Italy;[7] 3.7% per year in 1998-2011 in Netherlands;[34] 3.7% in 1975-2012 in Spain;[31] and, 3.9 in EURODIAB countries).[49] In the US, in 2002-2012 (about the same period as we studied), the APC of T1D was 1.8% ($p<0.001$) and that of T2D was 4.8% ($p<0.001$).[50] We found two periods with distinct patterns of pediatric diabetes in Ontario in the studied period. In 2004-2008, there

was a significantly rapid increase of diabetes incidence at 6% per year, with the highest increase of 10% per year in boys (0-6 years). Some authors suggested that the increased incidence in the younger age group may simply reveal an earlier age of diabetes onset.[51,52] Because we found a simultaneous increase of diabetes IR across all age groups in our study we are inclined to agree with other authors[5,31] that most probably we observed a real increase in the diabetes incidence in addition to a possible shift of diabetes onset to a younger age.

According to our findings, the overall increase of diabetes incidence in Ontario children in 2009-2012 was non-significant (1% per year, p=0.99). It was comprised of a declining diabetes incidence in boys (7-12 years; 4% per year); a stabilizing trend in boys (0-6 and 13-18 years; less than 1% of annual increase) and an increase at 2% per year in youth girls (7-18 years). These findings are similar to the diabetes incidence trends reported by other population-based studies. For example, the stabilizing trend of diabetes IR that we found in 2009-2012 in Ontario children was similar to the flattening of the diabetes IRs reported for Sweden,[6] Finland,[7] Norway,[8] Netherlands, Italy[32] and Czech Republic.[9] On the other hand, the rapid increase of diabetes incidence in boys (0-6 years) in 2004-2008 in Ontario was similar to reports from Newfoundland and Labrador, where significantly more boys were diagnosed with T1D than girls in the 0-4 year age group. It was suggested that a rapidly increasing incidence cannot be explained by genetic susceptibility alone but may be due to environmental, lifestyle, and epigenetic factors.[53]

Some authors suggested that a potential "residual misclassification of prevalent cases as incident cases" in a diabetes registry based on administrative rather than clinical data may affect the data on diabetes incidence and explain a decreasing trend in diabetes incidence.[54] However, our study

and previous Ontario studies based on the same diabetes provincial registry indicated the steadily increasing diabetes incidence over the 15-year period (from 1994 to 2008), while the declining trend started only in 2009 and lasted the following four years. A future study is required to analyze the diabetes incidence in Ontario children from 2012 until present in order to understand whether the diabetes incidence in this population continues declining or the long-term trend may be sinusoidal, consisting of regular peaks and troughs, as it was reported by an Australian study.[36]

Study strength and limitations. The strength of our study is in the use of the provincial registry of diabetes cases that were defined with the validated algorithm of diabetes incident case ascertainment. The main limitation of our study is an inability to distinguish between T1D and T2D cases and assess trends separate for each type of diabetes. A linkage of the diabetes registry with the provincial drug prescription data (e.g., insulin, oral hypoglycemic agents) may help to distinguish T1D from T2D as it has been done in British Columbia. Previous studies showed that ethnicities (Indigenous, Asian, and so on) are a strong predictor of T2D; however, our data did not contain data on children's ethnicities. It is likely that our data was also missing Indigenous on-reserve population that is known to be at high risk of diabetes. Due to the privacy requirements, age was available only in the aggregated format. Privacy requirements also put restrictions on how regions were defined for our analysis (14 LHINs were combined in four regions). Future studies at the single LHIN level may provide more findings to inform health services planning.

Conclusions

Recent pediatric diabetes incidence in Ontario was among the highest in the world between 2004 and 2012, with important age and geographic differences. A steadily growing trend of diabetes incidence, particularly among young boys (0-6 years of age) was observed in 2004-2008 and confirms earlier reports from other Ontario studies. However, the pediatric diabetes IR appears to plateau in 2009-2012 similar to some European countries. Similar to other countries, youth age group (13-18 years) is at the highest risk of diabetes, with a growing trend among youth girls (13-18 years) and a stabilized incidence rate among youth boys (13-18 years). To inform prevention of diabetes in children and youth, future research is needed to assess whether these trends persisted over the next six years until current time (2013-2018), distinguishing between T1D and T2D.

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Chapter 4

Paper 2. A population-based retrospective cohort study of hospital admissions for diabetic ketoacidosis (DKA) at diabetes diagnosis in children (0-18 years) in Ontario, Canada in 2004-2012

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Abstract

Purpose: To evaluate time trends and socio-demographic characteristics associated with the prevalence of diabetic ketoacidosis (DKA) hospital admissions at diabetes diagnosis in children aged 0 -18 years in Ontario, Canada in 2004-2012.

Methods: We conducted a retrospective cohort study using Ontario provincial registry person-level data for children (0-18 years) newly diagnosed with diabetes type 1 and 2, from April 1, 2004 through March 31, 2012 linked to the records in the national hospital discharge database. Outcome was DKA hospital admission at diabetes diagnosis. Poisson regression models were used to assess time trends and annual adjusted estimates of prevalence of DKA hospital admissions at diabetes diagnosis by geographic regions and for the entire province. Regional DKA prevalence rates were standardized to the Ontario population of children (0-18 years) in 2012. Multivariable binary logistic regression was used to assess the likelihood of DKA hospital admission at diabetes diagnosis (yes/no) in association with patient's age group at diagnosis (0-6, 7-12, and 13-18 years), sex, geographic region (South-Western, South-Eastern, South-Central, and Northern), rural community, and indicators of material deprivation and ethnic concentration of child's residence.

Results: Among 10,617 children diagnosed with diabetes, 15.5% were diagnosed during a hospital admission for DKA. The provincial and regional DKA prevalence rates did not change significantly over the nine-year period from 2004 to 2012 (p_{trend} =0.99). Younger children (0-6 years and 7-12 years) were at higher risk of DKA hospital admission at diagnosis of diabetes

than 13-18 years old youth (adjusted odds ratio (OR) 2.5 95% CI 2.2-2.8 and 2.1 95% CI 1.9-2.4, respectively). There were significant within-province regional differences in prevalence of DKA hospital admission at diabetes diagnosis after adjustment for age group, sex, material deprivation and ethnic concentration. South-Western Ontario had the highest (17.2%) and Northern Ontario had the lowest (13.7%) DKA prevalence rate, with adjusted OR=1.3, 95% CI 1.0-1.6. In young children (0-6 years), the likelihood of DKA at diabetes diagnosis was associated with indicators of material deprivation (OR 1.9 95% CI 1.4-2.5 for “most deprived” versus “least deprived”). In the older age group (13-18), boys were more likely to be hospitalized for DKA at the time of diabetes diagnosis than girls (OR 1.4 95% CI 1.1-1.7).

Conclusions: Prevalence of DKA hospital admissions at diabetes diagnosis in Ontario children is among the lowest in the world. Prevention of DKA should consider age-specific factors of DKA at diabetes diagnosis. Higher prevalence of DKA hospital admissions at diabetes diagnosis in children residing in some geographic parts of the province or most deprived communities despite the universal access to government-funded health care warrants further research.

Introduction

Diabetic ketoacidosis (DKA), a life-threatening acute complication of diabetes, is the leading cause of mortality and disability in children with diabetes.[1-5] DKA is caused by a severe insulin deficiency and an increase in counter regulatory hormones (i.e., glucagon, catecholamines, cortisol, and growth) that work against the action of insulin. This leads to the increased production of glucose and accumulation of chemicals (ketones) in blood and urine, causing life-threatening levels of acidosis and dehydration.[1,5,6] DKA is classified into mild, moderate and severe cases, depending on the severity of the acidosis.[1,6] The majority of children with moderate DKA and all children with severe DKA require hospitalization.[6] DKA has negative health consequences such as impairment of IQ and short-term memory due to acute reductions of brain volume.[1,7,8] DKA significantly increases the cost of initial diabetes care.[9,10] There is agreement that prevention of DKA should be a goal in managing pediatric diabetes.[1,5,6]

DKA is often the presenting symptom of new cases of diabetes due to a delayed diagnosis.[11] The prevalence varies from the lowest of 14% in Sweden and the highest of 80% in the United Arab Emirates.[12] Compared to other countries, Canada has one of the lowest frequencies of pediatric DKA at the time of diabetes diagnosis (18.6%, including both diabetes types).[13] Over the last 15 years, DKA hospitalization rates remained stable compared with non-DKA hospitalization rates that have decreased over time.[13-20] In the US, the frequency of DKA at diabetes diagnosis has remained as high as 29-30% in children and youth with type 1 diabetes (T1D) (n=5615) between 2002 and 2010.[17] A similar trend was observed in Europe. For example, in Austria, the prevalence of DKA at diabetes diagnosis remained high in children and youth with T1D (n=4038): 38% in 2005-2009 and 37% in 2010-2011.[18,21] In New Zealand, DKA prevalence at

diabetes diagnosis has declined from 42% in 1995-1996 to 27% in 1999-2013.[19] DKA in children at the onset of type 2 diabetes (T2D) is also reported, but it is less common than in the case of T1D.[17] One Canadian study reported that 11% of children with T2D (n=120) in Manitoba and Northwestern Ontario had episodes of DKA in 1986-1999.[4] In the US, DKA frequencies in youth with T2D (n=1425) decreased from 12% in 2002-2003 to 6% in 2008-2010 (p=0.001).[17] Updates on pediatric DKA trends are available from longitudinal projects in the US and Europe.[22] However, despite serious negative consequences for child's health and the high cost of inpatient care for DKA there has been no research on the pediatric DKA trends in Canada in the last fifteen years.

Protective factors of DKA at diabetes diagnosis are well documented: having a first degree relative with diabetes; parents with higher education; living in area with a higher background incidence of diabetes; and being diagnosed at a hospital that has a diabetes team.[23] Children younger than three years of age; those from ethnic minority or migrant groups; without medical insurance (in the US); and with a lower body mass index are at high risk of DKA at diabetes diagnosis.[23] Low family income was associated with the increased risk of DKA at diabetes diagnosis not only in the US, but also in Canada that have universal access to health care that should eliminate financial barriers to access.[13] Whether the association of DKA risk with family income persisted in Canadian children in the last 15 years, is not known. The extent to which rural residence contributes independently to the risk of DKA at diabetes diagnosis in Canadian children is also not clear. Research in Sweden, Lithuania, and Finland did not find significant differences in DKA frequency among children living in cities, towns, suburbs, or villages and rural areas.[24,25] However, findings from northern European countries cannot be extended to

Canadian pediatric diabetic populations due to the differences in geography (e.g., Canadian northern regions occupy extremely vast territory)[26] and population composition (e.g., higher proportion of immigrant population in Canadian larger cities[27] and Indigenous population in northern regions)[28].

The purpose of this study was to address the identified gap in the Canadian literature about trends and factors of DKA at diabetes diagnosis by examining characteristics of Ontario children who were hospitalized for DKA at the time of diabetes diagnosis in 2004-2012. Ontario is the most populous Canadian province of more than 13 million of people, accounting for almost 40% of the country's population,[29] and the second largest province in area covering more than one million square kilometres. The province has the population of 2.9 million children aged 0-18 years and one of the highest pediatric diabetes incidence in the world.[30]

Methods

We used a population-based retrospective cohort design. A pediatric diabetic cohort was identified in the Ontario Diabetes Database (ODD), a provincial diabetes registry based on health administrative data that is systematically collected by the provincial government, and linked to hospital admissions data from the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD). The linked and de-identified data was requested from the Institute for Clinical Evaluative Sciences (IC/ES) and accessed through a secure virtual desktop infrastructure (VDI). The Research Ethics Board of Laurentian University approved this study (file 6009778).

Study cohort. Ontario children, who were 1) less than 18 years old in line with a provincial definition of children for pediatric health services eligibility, 2) lived in Ontario and 3) received a

new diagnosis of diabetes (index event) during the period from April 1, 2004 through March 31, 2015 were included into our study cohort. In the ODD, the date of the diabetes diagnosis (index event) was identified using data on the Ontario Health Insurance Plan (OHIP) physician billing claims with a case definition algorithm that requires four physician claims over a two-year period.[31] The algorithm has a specificity of 98.9% and a sensitivity of 82.8% and was previously validated for Ontario children (0-19 years, n=923).[31] The available OHIP data does not allow distinguishing between diabetes types. Therefore, our analysis was performed for diabetes types 1 and 2 combined. Children who moved out of province or died before March 31, 2015 or did not have residence postal codes were excluded.

Variables. For each child in the study cohort, hospital admissions for DKA (outcome variable) that were recorded on the same or next day following the index event were identified in CIHI DAD using ICD-10-CA codes for DKA (E10.0 and E11.0). In addition to clinical data regarding diagnoses, procedures, and physician providers, the CIHI-DAD includes data on patient demographics and location of residence. Data on year of diabetes diagnosis, age group at diagnosis (0-6, 7-12, 13-18 years of age), sex, and indicators of material deprivation and ethnic concentration based on Ontario Marginalization Index (ON-Marg) were available for each child. We used ON-Marg quintile scores at the level of dissemination area that is the smallest stable geographic unit composed of one or more neighbouring dissemination blocks, with a population of 400 to 700 persons.[32] Quintile values range from 1 (“least” deprived or ethnic concentration) to 5 (“most” deprived or ethnic concentration). Material deprivation index reflects the proportion of population without a high school diploma; families who are lone parents; population with low

income; unemployed and on government assistance. Ethnic concentration reflects the percentage of recent immigrants (less than five years) and those who self-identify as visible minorities.[32]

Child's location of residence was described by a) geographic region (South-Western, South-Central, South-Eastern and Northern Ontario) and b) rural community (yes/no). Boundaries for four geographic regions were based on 14 Ontario Local Health Integration Networks (LHINs), organized for health care administrative, management and funding purposes.[33] South-Western Ontario included Erie St. Clair, South West, Waterloo Wellington, and Hamilton Niagara Haldimand Brant LHINs; South-Central Ontario included Central West, Toronto Central, Central, and Central East LHINs; South-Eastern Ontario included South East and Champlain LHINs; and Northern Ontario included North East and North West LHINs. Rural community was defined as a community with population of less than 10,000 people located outside urban areas, i.e., Census Metropolitan Agglomerations (CMAs) and Census Agglomerations (CAs).[34]

Statistical analysis. Statistical analysis was performed using SAS software, v.9.3 of the SAS System for Windows (©2011 SAS Institute Inc., Cary, NC, USA). Prevalence of DKA hospital admissions at diabetes diagnosis (%) was calculated with an annual number of children hospitalized for DKA at diabetes diagnosis as a numerator and an annual number of all children newly diagnosed with diabetes as a denominator, multiplied by 100. We performed the following analyses of DKA hospital admission prevalence: first, we examined time trends of the DKA prevalence over the nine-year period (2004-2012) at the regional level using a Poisson regression model for each of the four regions and the entire province, with the annual age-and-sex standardized prevalence as a dependent variable and year as an independent variable. DKA

prevalence rates for four regions were standardized to the Ontario population of children (0-18 years) in 2012 using a direct method.

Second, we computed provincial estimates of DKA hospital admission prevalence at diabetes diagnosis using a Poisson regression model with the DKA prevalence as a dependent variable adjusted for year, age group at diagnosis, sex and geographic region (independent variables). We also performed analysis of DKA occurrence at the individual level: first, we described socio-demographic characteristics of children who had hospital admission for DKA at diabetes diagnosis in comparison with the entire study cohort, including age group, sex, geographic region, rural community, material deprivation and ethnic concentration quintiles. We used binary logistic regression to estimate association of the likelihood of DKA hospital admission at diabetes diagnosis at the individual level (yes/no) with age group, sex, geographic region, rural community, material deprivation and ethnic concentration of the patient's residence. To identify age-specific predictors of DKA hospital admissions at diabetes diagnosis we computed binary logistic regression models for each of the three age groups (0-6, 7-12, and 13-18). All of the tests were two-sided and a p value of less than 0.01 was considered statistically significant.

Results

Between 2004 and 2012, a total of 10,617 children younger than 18 years of age were newly diagnosed with diabetes in Ontario. Of these, 1664 (15.5%) were diagnosed with diabetes during a hospital admission for DKA. The observed annual DKA hospital admission prevalence at diabetes diagnosis (%) varied from year to year; however, the overall changes in the prevalence by year were not significant over the studied period (Table 4-1).

Table 4-1: Prevalence of DKA hospital admissions at diabetes diagnosis by Ontario region in 2004-2012, [a] %

	2004	2005	2006	2007	2008	2009	2010	2011	2012	P_{trend} [b]
Ontario (n=10,617)	16.8	16.2	16.2	15.6	17.5	13.9	17.1	15.5	19.1	0.99
South-Central (n=5236)	15.7	16.7	15.2	14.4	17.7	14.3	14.5	15.2	19.5	0.99
South-Eastern (n=1387)	11.0	14.5	13.0	20.3	14.4	11.0	22.2	15.2	19.0	0.16
South-Western (n=3247)	20.3	17.5	18.7	16.0	19.8	15.5	19.6	15.9	19.6	0.99
Northern (n=747)	21.5	7.1	16.9	12.8	10.5	10.5	14.3	18.7	12.9	0.42

Notes: DKA = Diabetic Ketoacidosis.

[a] Age-and-sex standardized to the Ontario population of children in 2012.

[b] P-values were computed with Poisson regression models with DKA hospital admission prevalence as a dependent variable and year as an independent variable.

Poisson adjusted estimates of DKA hospital admission prevalence rates also indicated no significant changes by year over the studied period (p=0.12)(Table 4-2). Age group was a significant predictor of DKA hospital admission at diabetes diagnosis (p<0.0001) with higher DKA prevalence in younger children (20.5% for 0-6 years old and 18.0% for 7-12 years old) than in older youth (9.4% in 13-18 years old)(Table 4-2). Across geographic regions, the largest DKA prevalence was in South-Western Ontario (17.2%) and the smallest one was in Northern Ontario (13.7%). Sex was not associated with the DKA hospital admission prevalence (Table 4-2).

We assessed how the likelihood of DKA hospital admission at diabetes diagnosis was associated with socio-demographic characteristics of a child, including age group, sex, geographic region, residence in rural community and indicators of material deprivation and ethnic concentration (Table 4-3). Younger children (0-6 years) had a 250% higher odds ratio (OR) of DKA than youth (13-18 years) and children (7-12 years) had almost a 200% higher OR than the older age group (13-18 years)(p<0.0001)(Table 4-3). Multivariable binary logistic regression models for each of the three age groups identified age-specific characteristics of children who had DKA hospital admission at diabetes diagnosis (Table 4-4). The youngest children (0-6 years) from the most deprived neighbourhoods had almost a 200% higher OR than those from the least deprived areas (adjusted OR=1.9, 95% CI 1.4-2.5). Sex was a significant factor of DKA at diabetes diagnosis among the oldest group (13-18 years), where boys had a 40% higher risk than girls (adjusted OR=1.4, 95% CI 1.1-1.7).

Table 4-2: DKA hospital admission prevalence at diabetes diagnosis (Poisson model adjusted estimates), %

	DKA prevalence LSM (95% CI)	Parameter Estimates Exp (estimate) (Wald 95% CI)	Wald Chi-Square	P-value
Intercept		12.5 (10.5 - 15)	801.28	<0.0001
Year				
2004	15.1 (12.8-17.9)	0.8 (0.7 - 1)	2.42	0.12
2005	14.4 (12.2-17.1)	0.8 (0.7 - 1)	3.98	0.05
2006	14.8 (12.7-17.3)	0.8 (0.7 - 1)	3.41	0.07
2007	14.9 (12.8-17.4)	0.8 (0.7 - 1)	3.2	0.07
2008	16.9 (14.6-19.5)	0.9 (0.8 - 1.1)	0.3	0.58
2009	13.1 (11.1-15.3)	0.7 (0.6 - 0.9)	9.3	0.002
2010	15.5 (13.3-17.9)	0.9 (0.7 - 1.1)	2.11	0.15
2011	14.4 (12.3-16.8)	0.8 (0.7 - 1)	4.52	0.03
2012	17.8 (15.5-20.5)	1	.	.
Age group				
0-6 years old	20.5 (18.6-22.6)	2.2 (1.9 - 2.5)	141.38	<0.0001
7-12 years old	18.0 (16.5-19.7)	1.9 (1.7 - 2.2)	109.34	<0.0001
13-18 years old	9.4 (8.5-10.5)	1	.	.
Sex				
Girls	15.2 (14.0-16.5)	1 (0.9 - 1.1)	0.02	0.89
Boys	15.1 (13.9-16.4)	1	.	.
Geographic region				
South-Central	15.0 (13.9-16.1)	1.1 (0.9 – 1.4)	0.72	0.40
South-Eastern	15.0 (13.1-17.2)	1.1 (0.9 – 1.4)	0.57	0.45
South-Western	17.2 (15.8-18.7)	1.3 (1.0-1.6)	4.43.	0.03
Northern	13.7 (11.2-16.7)	1	.	.
Model characteristics	Value=204.7 DF=201		Value/DF *1.0*	

Notes: DKA = Diabetes Ketoacidosis, LSM =least squared mean, CI = confidence interval.

[a] Regression statistics for Type III analysis: year (df=8, Chi-square=12.9, p=0.12), age group (df=2, Chi-square=177.9, p<0.0001), sex (df=1, Chi-square=0.02, p=0.89), and geographic region (df=3, Chi-square=8.7, p=0.03).

Table 4-3: DKA hospital admission prevalence at diabetes diagnosis by socio-demographic groups

	Study cohort		DKA hospital admission		Prevalence	OR[a]	95% CI	P-value
	N	%	n	%	n/N, %			
All	10,617	100	1644	100	15.5			
Age group								
0-6	2472	23.3	527	32.1	21.3	2.5	2.2-2.8	<0.0001
7-12	3690	34.7	685	41.7	18.6	2.1	1.9-2.4	<0.0001
13-18	4455	42.0	432	26.3	9.7	1.0	Reference	
Sex								
Girls	5087	47.9	788	47.9	15.5	1.0	0.9-1.1	0.75
Boys	5530	52.1	856	52.1	15.5	1.0	Reference	
Geographic region								
South-Central	5236	49.3	771	46.9	14.7	1.1	0.9-1.5	0.40
South-Eastern	1387	13.1	211	12.8	15.2	1.1	0.8-1.4	0.50
South-Western	3247	30.6	564	34.3	17.4	1.3	1.0-1.7	0.04
Northern	747	7.0	98	6.0	13.1	1.0	Reference	
Rural community								
Yes	1421	13.4	214	13.0	15.1	1.0	0.9-1.2	0.70
No	9196	86.6	1430	87.0	15.6	1.0	Reference	
Material deprivation								
1 (least deprived)	2731	26.1	444	27.3	16.3	1.0	Reference	
2	2370	22.7	343	21.1	14.5	0.9	0.8-1.1	0.20
3	2058	19.7	306	18.8	14.9	1.0	0.8-1.1	0.70
4	1633	15.6	254	15.6	15.6	1.0	0.8-1.2	0.90
5 (most deprived)	1658	15.9	281	17.3	17.0	1.1	1.0-1.4	0.10
Ethnic concentration*								
1 (least ethnic)	1180	11.3	162	10.0	13.7	1.0	Reference	
2	1604	15.4	258	15.8	16.1	1.2	1.0-1.5	0.10
3	1826	17.5	295	18.1	16.2	1.2	1.0-1.5	0.20
4	2206	21.1	374	23.0	17.0	1.2	1.0-1.5	0.05
5 (most ethnic)	3634	34.8	539	33.1	14.8	1.1	0.9-1.4	0.50

* n=167 missing for material deprivation and ethnic concentration indices.

Notes: DKA = Diabetic Ketoacidosis, OR = Odds Ratio.

[a] Assessed using binary logistic regression with the DKA occurence (yes/no) as a dependent variable and age group, sex, geographic region, rural community, material deprivation and ethnic concentration as independent variables.

Table 4-4: Predictors of DKA hospital admission at diabetes diagnosis by age group

	Age group					
	0-6 years n=2472		7-12 years n=3690		13-18 years n=4455	
	OR	95%CI	OR	95%CI	OR	95%CI
Sex						
Girls	1.0	Reference	1.0	Reference	1.0	Reference
Boys	0.9	0.7-1.0	0.9	0.7-1.0	1.4**	1.1-1.7
Geographic region						
South-Central	1.7	1.0-2.9	0.9	0.6-1.4	1.0	0.7-1.6
South-Eastern	1.5	0.9-2.7	0.9	0.6-1.4	1.1	0.6-1.7
South-Western	1.8	1.1-3.0	1.2	0.8-1.7	1.2	0.8-1.9
Northern	1.0	Reference	1.0	Reference	1.0	Reference
Rural community						
Yes	0.9	0.7-1.3	1.0	0.7-1.3	1.2	0.9-1.7
No	1.0	Reference	1.0	Reference	1.0	Reference
Material deprivation ‡						
1 (least deprived)	1.0	Reference	1.0	Reference	1.0	Reference
2	1.1	0.9-1.5	0.8	0.6-1.0	0.9	0.7-1.2
3	1.0	0.7-1.3	1.0	0.8-1.3	0.9	0.7-1.2
4	1.3	0.9-1.7	0.9	0.7-1.2	0.9	0.6-1.2
5 (most deprived)	1.9***	1.4-2.5	1.0	0.8-1.3	0.8	0.6-1.1
Ethnic concentration‡						
1 (least concentrated)	1.0	Reference	1.0	Reference	1.0	Reference
2	1.2	0.8-1.7	1.2	0.9-1.7	1.2	0.8-1.8
3	1.0	0.7-1.5	1.2	0.9-1.8	1.2	0.8-1.8
4	1.0	0.7-1.5	1.4	1.0-2.0	1.3	0.9-1.9
5 (most concentrated)	0.9	0.6-1.4	1.3	0.9-1.8	1.0	0.7-1.5

Notes: DKA=Diabetic Ketoacidosis, OR= Odds Ratio.

‡ missing n=167. **p<0.01 ***p<0.0001**hospital admission prevalence**

Discussion

Our study showed that in 2004-2012 the DKA hospital admission prevalence at diabetes diagnosis was 15.5% in Ontario children (0-18 years). It was lower than the prevalence reported in Ontario in 1994-2000 (18.6%)[13] and in Newfoundland and Labrador (22.1%, only T1D) in 2007-2011.[35] DKA at diabetes diagnosis in Ontario children is less frequent than in children and youth in other developed countries, including Germany (21%);[15] New Zealand (27%);[19] the US (29-31%);[17] Israel (29%);[36] and France (44%).[37] A reduction of DKA hospital admissions prevalence at diabetes diagnosis in Ontario children in the studied period compared with 1994-2000 may be attributed to the Ontario Paediatric Diabetes Network (OPDN), implemented in 2001 to improve access to specialized pediatric diabetes care by connecting local health care providers across the province with pediatric specialists in diabetes in five tertiary centres.[38]

During the study period of 2004-2012, the prevalence of DKA hospital admissions at diabetes diagnosis did not change significantly in Ontario children (0-18 years). This finding is consistent with stable trends in DKA reported in other countries, including the US in 2002-2010,[17] Austria in 1989-2011,[18] New Zealand in 1999-2013,[19]Poland in 2006-2014,[20] and Germany in 1995-2009.[15] The reason for the stable DKA prevalence at diabetes diagnosis in recent years is unclear. We suggest that research using qualitative methodology and involving children parents, caregivers and health care providers may help to understand pathways from the first diabetes symptoms leading to DKA diagnosis in children. Such knowledge may inform targeted interventions to prevent DKA at diabetes diagnosis and reduce negative consequences of this complication on children's health.

Previous studies showed that un-insured children with diabetes in the US were more likely to present with DKA than insured children, and their condition tended to be more severe and life threatening compared to children who were insured.[39] Poor access to health care and low community and physician awareness of pediatric diabetes were seen as major factors contributing to this trend. In contrast, our study showed that the likelihood of DKA at diagnosis in Ontario children was not associated with material deprivation. Similarly, it was not associated with rural residence and the level of ethnic concentration in child's residence area. These findings may be explained by universal access to the initial diabetes care available for all Ontario children.

Consistent with numerous other studies, younger age was associated with increased risk of DKA at diabetes diagnosis in our study cohort.[23] Younger children were 2-2.5 times more likely to have DKA than youth (13-18 years). This may be related to a combination of factors leading to a delayed diabetes diagnosis and treatment, including more aggressive and faster metabolic deterioration in younger children[40] and shorter duration of symptoms at the onset of diabetes.[41] A limited ability to verbalize symptoms due to younger age may also contribute to a delayed diagnosis.[23] Our results indicated that material deprivation was a significant risk factor of DKA only among younger children (0-6 years) with children in the most deprived areas being at a higher risk of DKA at diagnosis than children in the least deprived areas. We suggest that this may be influenced by child's parental education rather than differences in access to the initial diabetes health care. Indeed, previous research showed that having parents with higher than secondary education was a protective factor against DKA at diabetes diagnosis.[24,40,42] Young children (0-6 years) are at a high risk of DKA due to their age and those of them who reside in

the most deprived areas are more likely to have parents without high school diploma, hence they may be less protected in this sense against acute diabetes complications such as DKA at the onset of diabetes. DKA is a preventable condition because most children present with classic symptoms.[1] Some studies reported a significant decrease in DKA frequency after education campaigns.[36,43,44] Our findings have an important implication for a targeted DKA prevention in Ontario, suggesting a need for increasing awareness among parents and physicians about diabetes symptoms, especially in young children and, particularly, in the most deprived neighbourhoods.

Consistent with other studies, our results showed that sex was not associated with the DKA at diabetes diagnosis in our entire study cohort.[23] However, boys 13-18 years were significantly more likely to present with DKA at diabetes diagnosis than youth girls. One possible explanation of this difference may be behavioral patterns of primary care use by adolescents, with girls being more frequent users of physician services for preventive and non-preventive care than boys. [45-47] Furthermore, a population-based US study showed that there was no association between sex and DKA at diagnosis for T1D patients; however, DKA was two times more frequent among teenage boys than girls with T2D.[17] This may suggest that the association of sex and DKA prevalence in the older age group in our study cohort was significant due to a possibly higher proportion of T2D cases among youth (13-18 years) than in younger group (0-12 years). Future studies distinguishing between the two types of diabetes in Ontario health administrative data are required to test this hypothesis.

Our study results indicated that Northern Ontario had the lowest prevalence of DKA hospital admissions at diabetes diagnosis in the province. According to the recent OPDN report, 31% of all OPDN pediatric patients in Northern Ontario had T2D, compared to only 4% in the rest of the province.[48] Considering that prevalence of DKA at diagnosis is less frequent in case of T2D than T1D, the lower than average DKA prevalence in Northern Ontario may be explained by a high proportion of children with T2D in this region compared to other regions.

Overall, our study showed that observed geographic differences in DKA prevalence at diabetes diagnosis were not statistically significant. However, these geographic variations do indicate that there is room for reduction of the DKA occurrence in some regions (e.g. South-Western Ontario, where the DKA rate was the highest in the province). Better understanding of factors contributing to these differences may provide insights into possibilities for a timely diabetes diagnosis and prevention of DKA. We suggest that a comparative analysis of DKA prevalence at diabetes diagnosis using health administrative data at the level of single LHINs and OPDN centres would be helpful in understanding health care delivery characteristics associated with the lower or higher DKA rates.

Our study has limitations related to the secondary use of health data that were collected for administrative purposes and thus may have biases.[49] For example, DKA episodes may be more accurate as they were recorded in hospital admissions data whereas identification of new diabetes cases were based on physician billing data that may be less accurate due to coding misclassification (OHIP database allows only one diagnostic code). Another limitation of available administrative hospitalizations data is inability of distinguishing between T1D vs T2D

in the analysis of DKA prevalence, time trends and contributing factors. Difficulties accessing health administrative data on certain populations (e.g., Indigenous, refugee and new immigrants to Canada) also pose limitations. Furthermore, there may be factors contributing to misdiagnosis of diabetes that were not captured in our data. For example, characteristics of primary health care providers (e.g., physician's specialty, model of practice, physician's years in practice, percentage of children among patients, etc.). The strength of the study stems from the use of population-based retrospective cohort research design and person-level linked data. This combination allows avoiding ecological fallacy by complementing study of time trends and prevalence of pediatric DKA hospitalizations at the regional level with assessing factors of pediatric DKA incidence at the individual level.

Conclusions

Prevalence of DKA hospital admissions at diabetes diagnosis in Ontario children is among the lowest in the world, yet opportunities for improvement were identified. These include the opportunity for targeted prevention of DKA in children younger than 7 years of age. Higher DKA prevalence in children residing in some geographic parts of the province or most deprived communities despite the universal access to government-funded health care warrants further research.

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Chapter 5

Paper 3. Effects of geographic region and physician services on diabetes ketoacidosis hospital admissions in Ontario children with established diabetes: a population-based longitudinal cohort study using health administrative data

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For submission to Canadian Medical Association Journal

Abstract

Purpose: To assess effects of geographic region and use of physician services on diabetes ketoacidosis (DKA) hospital admissions in Ontario children with established diabetes.

Methods: Population-based retrospective cohort study of person-level data from a hospital discharge database linked with physician services billing claims for Ontario children diagnosed with diabetes in 2004 to 2012. The unit of analysis was a person-year. Diabetes related physician visits (exposure) were identified for each person-year starting from 30 days after diabetes diagnosis up to March 31, 2015. The outcome was at least one DKA hospital admission in a person-year following the exposure. Generalized linear mixed-method modeling (GLMM) was used to assess effects of child's geographic region (Northern, South-Western, South-Central, or South-Eastern), specialty of main diabetes care physician (pediatric endocrinologist, pediatrician, family physician (FP)/general practitioner (GP), endocrinologist, or shared pediatrician and FP/GP) and frequency of diabetes related physician visits on the outcome variable. Models were adjusted for sex, age group, material deprivation, comorbidity, duration of diabetes, rural residence, diabetes related emergency department (ED) visits and psychiatrist visits.

Results: The study cohort consisted of 8687 children, with 51,693 person-years of observations in the follow-up period. The unadjusted annual DKA hospital admission rate across Ontario was 3.6% (1842/51,693 person-years), with the highest rate in South-Western Ontario at 4.2% (657/15,657 person-years) and the lowest rate in South-Eastern Ontario at 2.7% (193/7141 person-years)($p< 0.0001$). The adjusted effect of geographic region on DKA hospital admissions

was significant ($p< 0.05$) until comorbidity was added to the model ($p=0.27$). Children who saw pediatric endocrinologists did not experience the effect of comorbidity on DKA hospital admission (OR=1.07 95% CI 0.5-2.5). However, the adjusted OR for children with comorbidities compared to children without comorbidity was 2.18 (95% CI 1.77-2.69) for those cared by pediatricians, 2.26 (95% CI 1.49-3.45) for children cared by endocrinologists, 3.8 (95% CI 2.62-5.51) for children cared by FP/GPs and 4.47 (95% CI 2.94-6.79) for those who did not see any physician for diabetes care. Children with psychiatrist visits were more likely to have DKA hospital admission than children without psychiatrist visits ($F=23.12$, $p< 0.0001$). This effect was significantly larger in children residing in rural areas (OR=4.2 95% CI 2.0-8.5) than in urban centres with population of more than 100,000 (OR=1.4 95% CI 1.1-1.9) or urban centres with population of 10,000-99,999 (OR=2.2 95% CI 1.1-4.3). Older age, female sex, material deprivation, at least one diabetes-related ED visit and frequent diabetes-related physician visits were associated with higher odds of DKA hospital admission.

Conclusions: Our study showed that hospital admissions for DKA among Ontario children with established diabetes were less frequent than in other developed countries; however, within the province there were inequities in the rates of pediatric DKA hospital admission and use of subspecialist (pediatric endocrinologist) services based on geographic region. Our findings suggest that improvements of access to pediatric endocrinologists, particularly for children with comorbidities, and access to mental health services, particularly for children with diabetes residing in rural areas, may prevent DKA and negative consequences of this condition on health of children with diabetes.

Introduction

Diabetic ketoacidosis (DKA), a life-threatening acute complication of diabetes, is the leading cause of mortality and disability in the pediatric diabetic population.[1-5] DKA usually results in admission to the hospital, adds a significant burden to patients and families, and is also associated with considerable costs to health care.[6-8] Rates of DKA in children with diabetes vary between and within countries, from 13% to 80% at the time of diagnosis[9] and from 1% to 15% per patient per year in children with established diabetes.[10-12] Poor diabetes management is one of the major immediate causes of DKA in children with established diabetes.[5,13-16] Certain pediatric populations have higher risk of DKA, including children with longer duration of the disease or a previous DKA admission; adolescent girls; children with psychiatric disorders; and children with lower parental income and educational level.[1] To ensure the best health outcomes, children with diabetes require comprehensive care, including specialized medical care provided by either a pediatric endocrinologist or pediatrician with diabetes expertise; education provided by dietitian and diabetes nurse educator; and, support from social worker and mental health professional.[17,18] There is evidence from the USA that comprehensive diabetes care may reduce the risk of DKA in children.[19]

Canada has universal health care insurance that should eliminate financial barrier to access; however, pediatric DKA rates in Canadian children with diabetes vary depending on parental income[13] and place of residence.[20,21] Canadian studies revealed differences in quality of pediatric diabetes care and adherence to clinical practice guidelines dependent on place of residence (rural versus urban) and diabetes care provider (generalist (FPs/GPs and pediatricians versus pediatric physician specialists). [22,23] In British Columbia, a population-based study showed that children seeing family physicians (FPs)/general practitioners (GPs) without

specialist support for diabetes care had lower adherence to guidelines compared to those having specialists only (i.e., pediatricians, pediatric endocrinologists, adult endocrinologists, internist) or a combination of FP/GP and specialist visits. Whether this difference had any effect on health outcomes, including occurrence of acute diabetes complications such as DKA, has not been studied.[22] Substantive research on Canadian adults found that acute diabetes complications (including DKA) were potentially preventable by improvements in diabetes care. [24-30] However, because of important differences between child and adult diabetes, findings from research on adults may not be directly extended to pediatric diabetic populations.[5,18,31] Furthermore, systematic and population-based research on pediatric DKA is mostly focused on DKA at diabetes diagnosis,[9,13,15,32-36] while research on DKA in children with established diabetes received less attention in the literature.[35,37,38] To address the described gaps in the literature, we aimed to study DKA over time in children with established diabetes residing in Ontario (the most populous and the second largest province by area in Canada).

The province of Ontario has a population of 2.9 million children aged 0-18 years and one of the highest pediatric diabetes incidence in the world.[21] In 1991-1999, there was a 3.7-fold difference in age- and sex-adjusted pediatric DKA rates between district health councils (DHCs) with the highest and lowest DKA rates.[13,20] The highest DKA rates were reported in Algoma, Cochrane, Manitoulin and Sudbury DHCs in Northern Ontario region that does not have academic pediatric health centres (that provide pediatric specialized care and located in large urban centres) compared to other Ontario DHCs that have or are located in a relative proximity to academic pediatric centres.[20] This regional variation was similar to ones for asthma and gastroenteritis: the more populated urban areas had lower rates of hospital admissions for acute

complications of these chronic diseases compared to more remote and sparsely populated rural areas.[39,40]

To promote equitable and timely access to quality diabetes care for all children in Ontario, the Ontario Pediatric Diabetes Network (OPDN) was established in 2001.[41] More than 90% of children and youth with diabetes in the province receive diabetes care through the OPDN,[41] which consists of 30 specialized pediatric diabetes centers (PDCs) located across the province and linked to one of five academic PDCs in Ottawa, Toronto, London, Hamilton and Kingston. Each PDC has an interdisciplinary team of registered nurses, dietitians, and social workers with training in diabetes care working closely with physicians. Research has shown that availability of resources and services for children with diabetes varies substantially across the PDCs.[41] Specifically, the physician workforce serving PDCs varies from generalists (family physicians, pediatricians) to pediatric endocrinologists (at academic pediatric health centres). The impact of this variability on health outcomes is not known.

A recent study showed that despite an overall positive impact of the implementation of the OPDN on health outcomes, particularly for children with diabetes of lower socio-economic status and in urban areas; there was an increased disparity between urban and rural children in rates of emergency department (ED) visits and hospital admissions suggesting that rural children with diabetes did not benefit from improvement of diabetes care as much as urban children.[42] The reasons of this difference was not explored. In our study, we will address these questions by assessing how geographic location and rural residence may contribute to the risk of DKA in Ontario children with established diabetes. We will focus on DKA episodes that led to hospital

admission. The two research questions guiding this study are: (1) What are DKA hospital admission rates in children with established diabetes and patterns of their use of physician services for diabetes care across Ontario regions? and (2) What are the independent effects of geographic region and children's use of physician services for diabetes care on the likelihood of DKA hospital admission in Ontario children with established diabetes?

Methods

Study design

We conducted a population-based longitudinal cohort study of Ontario children diagnosed with diabetes between April 1, 2004 and March 31, 2012. The Research Ethics Board of Laurentian University approved this study (file 6009778).

Data sources

We obtained person-level de-identified data from the Institute of Clinical Evaluative Studies (ICES), including: (a) data from the Ontario Diabetes Database (ODD), a provincial registry of persons with diabetes, to identify our study cohort; (b) hospital admissions data from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI DAD); (c) physician fee for service claims data from the Ontario Health Insurance Plan (OHIP), and (d) ED records from the CIHI National Ambulatory Care Reporting System (NACRS). Record linkage was performed at ICES based on a patient's health care number. Our study was conducted for Type 1 and Type 2 diabetes combined because the available data sources do not distinguish between the two diabetes types.

Study cohort

Initial inclusion criteria were: 1) age younger than 18 years at the time of diabetes diagnosis in line with a provincial definition of children for pediatric health services eligibility, 2) a new diagnosis of diabetes in the period from April 1, 2004 through March 31, 2012, and 3) Ontario residency and eligibility for OHIP at the time of diabetes diagnosis and throughout the follow-up study period. New pediatric diabetes cases were identified at ICES with a previously validated case definition algorithm that requires four physician claims with diabetes code 250 or 1 OHIP fee code Q040, K029, K030, K045, K046 claim over a two-year period.[43] The algorithm has a specificity of 98.9% and a sensitivity of 82.8% validated for Ontario children (0-19 years, n=923).[43]

Outcome variable

The primary outcome was at least one DKA hospital admission identified as an in-patient claim with the International Classification of Diseases (ICD)-10-CA codes E10.0 and E11.0 in CIHI DAD. The outcome variable was binary with values of "1" for a positive outcome (at least one DKA hospital admission) and "0" for a negative outcome (no DKA hospital admission).

Geographic region

Child's geographic region was defined using the last OHIP registration address for each observed year. The geographic regions were: South-Western, South-Central, South-Eastern and Northern Ontario, defined using 14 Ontario Local Health Integration Networks (LHINs) (Figure 0.1). Ontario LHINs are units organized for health care administrative, management and funding purposes.[44] We combined them based on geographic location and according to the ICES data privacy requirement so that the number of individuals in each studied regional unit was large enough to avoid identification of individuals due to small count cells.

Main diabetes care physician provider

For each child in the study cohort and each year in the follow-up period (a person-year), we computed the number of physician visits claimed with the OHIP diabetes code 250 by provider's specialty recorded in the OHIP database (pediatrician, pediatric endocrinologist, family physician /general practitioner (FP/GP), and endocrinologist). Main diabetes care physician provider was defined as the physician with whom the child had 50 or more percent of all diabetes related visits.[45] In cases when a pediatrician and a pediatric endocrinologist combined provided more than 50% of diabetes care, the main diabetes care provider was coded as a pediatric endocrinologist to capture the use of pediatric sub-specialist care. Similarly, when an endocrinologist and an FP/GP combined provided more than 50%, the main diabetes care provider was coded as an endocrinologist. A sensitivity analysis of this grouping showed that the combining of shared care with specialist or sub-specialist care did not have effect on the outcome variable. First, frequency of the outcome variable was not different for specialist or sub-specialist and respective shared care groups. Second, there were small percentages of shared care in our data, e.g., pediatrician plus pediatric endocrinologist (1.5% of all person-years) and FP/GP and endocrinologist (0.8% of all person-years). In all other cases, the main diabetes care provider was coded as "shared FM/GP and pediatrician". If no physician claims with diabetes code 250 were recorded, then the main diabetes care provider was coded as "none".

Frequency of diabetes related physician visits

In line with the Canadian and international clinical practice guidelines (CPGs) that suggest quarterly diabetes routine visits[17,18,46] and Canadian pediatric endocrinologists' suggestions of optimal level of adherence to the CPGs (3 diabetes related visits),[22] we classified frequency of

diabetes physician visits in three categories: “below optimal” (0-2 visits/person-year), “near optimal” (3-5 visits/person-year) and, “frequent” (6 visits/person-year and more).

Diabetes management visits

We described frequency of physician visits marked with the OHIP diabetes management (DM) fee codes, i.e., K029, K030, K045 and Q040, with a variable that had three categories: “none”, “1 visit” and “more than one visit.”

ED visits for diabetes reasons

The number of ED visits marked with diabetes as “most responsible reason” in the CIHI-NACRS was computed for each person-year. The variable of ED visits was binary: “0” when no ED visits for diabetes care were recorded and “1” when at least one ED visit was recorded.

Covariates

We included person-level variables of age, sex, material deprivation indicators, and variables of comorbidity and mental problems in our analysis because previous studies indicated association of DKA hospital admission with these personal characteristics.[16,47] Age at the time of diabetes diagnosis was classified into 3 groups: 0-6, 7-12 and 13-18 years old. To account for the child’s age in the follow-up period, we used a variable of diabetes duration, which indicated the number of years since diabetes diagnosis in addition to the age group at diabetes diagnosis. We used the Ontario Marginalization (ON-Marg) quintile scores for material deprivation that are available at the level of dissemination area, (i.e., the smallest stable geographic unit composed of one or more neighbouring dissemination blocks, with a population of 400 to 700 persons).[48] Material deprivation quintile values range from 1 (least deprived) to 5 (most deprived). Material deprivation index reflects the proportion of the population without a high school diploma; families who are lone parents; population with low income; unemployed and on government

transfer payments. In our study, we used the ON-Marg defined for the child's place of residence at the time of diabetes diagnosis.

Child's community rural (or urban) status was defined using Statistics Canada's Statistical Area Classification (SAC) types.[49] This definition of rural and urban areas fits well population-based studies of health services use.[50] According to it, "rural" is defined as all area outside "large urban areas" or Census Metropolitan Areas (CMAs) and "urban areas" or Census Agglomerations (CAs). CMAs and CAs consist of one or more adjacent municipalities centred on a population centre (known as the core). A CMA has a total population of at least 100,000 of which 50,000 or more must live in the core. A CA has a core population of at least 10,000 and rural area has population of less than 10,000. Rural areas are further classified into four Metropolitan Influenced Zones (MIZs) (strong, moderate, weak or no influence) according to the percentage of residents commuting for work to urban cores (ranging from 30% in the strong MIZ to 0% in no MIZ).[49] In this study, all MIZ SAC types were considered as "rural" communities, CMAs as "large urban" and CAs as "urban" communities.

Charlson Comorbidity Index [51-53] was used to account for comorbidity at the time of diabetes diagnosis. The Charlson Index is based on identifying comorbidities using ICD codes in health administrative hospital data. This method was shown to be useful for pediatric population.[54] A binary variable was coded as "0" for children with no identified comorbidities and "1" for children with one or more comorbidities. At least one visit to a psychiatrist was used as a proxy indicator of possible psychiatric disorders and mental problems that are known to increase DKA

risk.[55] We used a binary variable for each person-year: "0" for no visits to a psychiatrist and "1" for one or more psychiatrist visits.

Statistical analysis

We compared socio-demographic characteristics of children with established diabetes and their use of health services for diabetes care between Ontario regions using Pearson chi-square tests. We calculated the rate of DKA hospital admissions in each 365-day period ("person-year") starting from day 30 after the diabetes diagnosis to allow for an initial period of "establishment" of diabetes diagnosis, including initial diabetes management education, until the cut-off date on March 31, 2015. We calculated crude DKA hospital admission rates as the number of person-years with at least one DKA hospital admission divided by the total number of person-years and expressed them in percentages (or, per 100 person-years). We used Pearson chi-square tests to assess the relationship of the crude DKA hospital admission rate with socio-demographic characteristics, use of health services for diabetes care and other covariates.

We used generalized linear mixed-method modeling (GLMM) with a binary distribution of the outcome variable and logit link function to assess the relationship between the DKA hospital admission outcome and explanatory variables (fixed effects in the models), including child's geographic region (i.e., Northern, South-Western, South-Central, or South-Eastern), specialty of the main diabetes care physician provider, and frequency of diabetes related physician visits. Subject variation was treated as a random variable. Models were adjusted for covariates, including duration of diabetes, socio-demographics (sex, age group, material deprivation, rural or urban community), and indicators of health status (comorbidity, ED and psychiatrist visits). We

used all characteristics of diabetes care health services (main diabetes care provider, frequency of diabetes physician visits, ED visits and psychiatrist visits) occurring in a preceding year. We started modeling with Model 1 that included only an intercept. In Model 2, we modeled effects of Ontario regions, adjusting for duration of diabetes. In Model 3, we adjusted DKA hospital admission likelihood for socio-demographic characteristics (i.e., age group at diagnosis, sex, material deprivation and rural or urban community). In Model 4, we added characteristics of diabetes care in the preceding year period (i.e., main diabetes care physician specialty, frequency of diabetes visits, and ED visits). Finally, in the full model 5 we additionally adjusted for health status indicators, i.e., comorbidity and psychiatrist visits. Odds ratios and 95% confidence intervals (CIs) were obtained by exponentiating the parameter estimates. All statistical analyses were performed using SAS software, v.9.3 of the SAS System for Windows (©2011 SAS Institute Inc., Cary, NC, USA).

Results

There were 10,706 Ontario children newly diagnosed with diabetes registered in the ODD from April 1, 2004 through March 31, 2012. We excluded cases of persons without valid residential postal code (n=7); who were not eligible for OHIP or moved out of province (n=33) or died (n=49) before March 31, 2015. We excluded from analyses 1930 persons who did not have physician claims with diabetes code in the entire study period. A higher percentage of excluded persons were in South-Western and Northern Ontario ($p=0.013$) and among the youngest (0-6 years of age) and oldest (13-18 years of age) age groups ($p<0.0001$). Distribution by sex, material deprivation, and rurality was not different among the excluded and included persons. The remaining 8687 persons comprised our study cohort, with a minimum of three and a maximum of 11 years of observations per person following diabetes diagnosis, comprising in total 51,693 person-years available for DKA hospital admission observations (Table 5-1).

Table 5-1: Total unique persons and person-years (annual observations) by year of diabetes diagnosis and follow-up year

Diabetes diagnosis in	Number of years since diagnosis									Person-years
	1-3	4	5	6	7	8	9	10	11	
2004	899	899	899	899	899	899	899	899	899	8990
2005	937	937	937	937	937	937	937	937		8433
2006	977	977	977	977	977	977	977			7816
2007	982	982	982	982	982	982				6874
2008	961	961	961	961	961					5766
2009	986	986	986	986						4930
2010	1019	1019	1019							4076
2011	956	956								2868
2012	970									1940
Number of persons:	8687	7717	6761	5742	4756	3795	2813	1836	899	51,693

Of 8687 persons, at the time of diagnosis, 7% (n=610) resided in Northern Ontario, 29.8% (n=2589) in South-Western Ontario, almost a half 49.8% (n=4324) in South-Central Ontario and 13.4% (n=1164) in South-Eastern Ontario. Of all children, 21.9% were younger than 6 years old and 47.7% were female (Table 5-2). The majority (78%) lived in CMAs (large urban areas), 9% in CAs (urban areas) and 13% lived in rural communities. More than 25% lived in the least deprived neighbourhoods and about 16% lived in the most deprived neighbourhoods. There were 37.8% of children who had one or more comorbidity at the time of diabetes diagnosis. Socio-demographic characteristics of children with diabetes differed between Ontario regions. Compared with other regions, Northern Ontario children with established diabetes were likely to be diagnosed at an older age 0-6 ($p< 0.0001$), had a higher proportion of females ($p= 0.006$), were living in rural communities ($p< 0.0001$) or the most deprived neighbourhoods ($p< .0001$), and were more likely to have comorbidities ($p< 0.0001$) (Table 5-2).

Table 5-2: Socio-demographic characteristics of the study cohort by Ontario region[a]

	All Ontario		Region			
			Northern	South-Western	South-Central	South-Eastern
	N	%	n (%)	n (%)	n (%)	n (%)
All study cohort	8687	100	610 (100)	2589 (100)	4324 (100)	1164 (100)
Age group at diagnosis						
0-6	1905	21.9	108 (17.7)	627 (24.2)	885 (20.5)	285 (24.5)
7-12	3265	37.6	232 (38.0)	977 (37.7)	1598 (37.0)	458 (39.4)
13-18	3517	40.5	270 (44.3)	985 (38.1)	1841 (42.5)	421 (36.1)
Sex						
Girls	4144	47.7	314 (51.5)	1171(45.2)	2076 (48.0)	583 (50.1)
Boys	4543	52.3	296 (48.5)	1418 (54.8)	2248 (52.0)	581 (49.9)
Community[b]						
Large urban	6743	77.6	226 (37.0)	1842(71.1)	3949 (91.3)	726 (62.4)
Urban	786	9.1	142 (23.3)	336 (13.0)	139 (3.2)	169 (14.5)
Rural	1158	13.3	242 (39.7)	411 (15.9)	236 (5.5)	269 (23.1)
Material deprivation[c]						
1 (least deprived)	2246	25.9	50 (9.1)	655 (25.7)	1167 (27.1)	374 (32.6)
2	1945	22.4	88 (16.1)	586 (22.9)	1001 (23.3)	270 (23.5)
3	1693	19.5	123 (22.5)	491 (19.2)	884 (20.6)	195 (17.0)
4	1305	15.0	150 (27.4)	421 (16.5)	598 (13.9)	136 (11.8)
5 (most deprived)	1360	15.7	136 (24.9)	401 (15.7)	650 (15.1)	173 (15.1)
Comorbidity						
None	5405	62.2	282 (46.3)	1378 (53.2)	2854 (66.0)	891 (76.5)
1 or more	3282	37.8	328 (53.8)	1211 (46.8)	1470 (34.0)	273 (23.5)

[a] Age group at diabetes diagnosis ($p<0.0001$), sex ($p=0.006$), community ($p<0.0001$), material deprivation ($p<0.0001$), comorbidity ($p<0.0001$).

[b] Defined using Statistics Canada Statistical Area Classification (SAC) codes: Large urban was defined as Census Metropolitan Areas (CMAs), with population 100,000 or greater, urban was defined as Census Agglomerations (CAs), with population 10,000-99,999; rural was defined as a community outside of CMAs or CAs, with population less than 10,000.

[c] Missing n=138.

In Northern Ontario, 25.7% of person-years did not have physician visits for diabetes care compared with 16.2-17.4% of person-years in other Ontario regions (Figure 5-1). South-Eastern Ontario had the smallest proportion of children with one or more comorbidities (23.5% versus 53.8% in Northern Ontario) and the largest proportion of children residing in the least deprived neighbourhoods (32.6% versus 9.1% in Northern Ontario) compared with other Ontario regions (Table 5-3).

Diabetes related physician services and indicators of health status by Ontario region

Main diabetes care physician provider.

In more than half of observed person-years (53.8%), pediatricians were main diabetes care physician providers for children in our study cohort (Figure 5-1). FPs/GPs were main diabetes care physician providers in 13% of person-years. Pediatric endocrinologists were main diabetes care providers in 4.3% person-years (in 0.8% they shared care with pediatricians). Endocrinologists were main diabetes care physician providers in 9.6% of person-years (in 1.5% they shared care with FP/GPs). There were 17.4% of person-years that had no diabetes-related physician visits. In 1.9% of person-years, physician diabetes care was provided by pediatricians and FP/GPs. There was a difference in main diabetes care physician providers between Ontario regions ($p < 0.0001$). In Northern Ontario, children were less likely to see pediatricians (47.1%) and pediatric endocrinologists (0.3%) for diabetes care and more likely to be seen by FP/GPs (18.9%) than in other Ontario regions. In contrast, South-Eastern Ontario children were most likely to see pediatric endocrinologists than in other parts of Ontario (25.3% versus 0.3-1.2%).

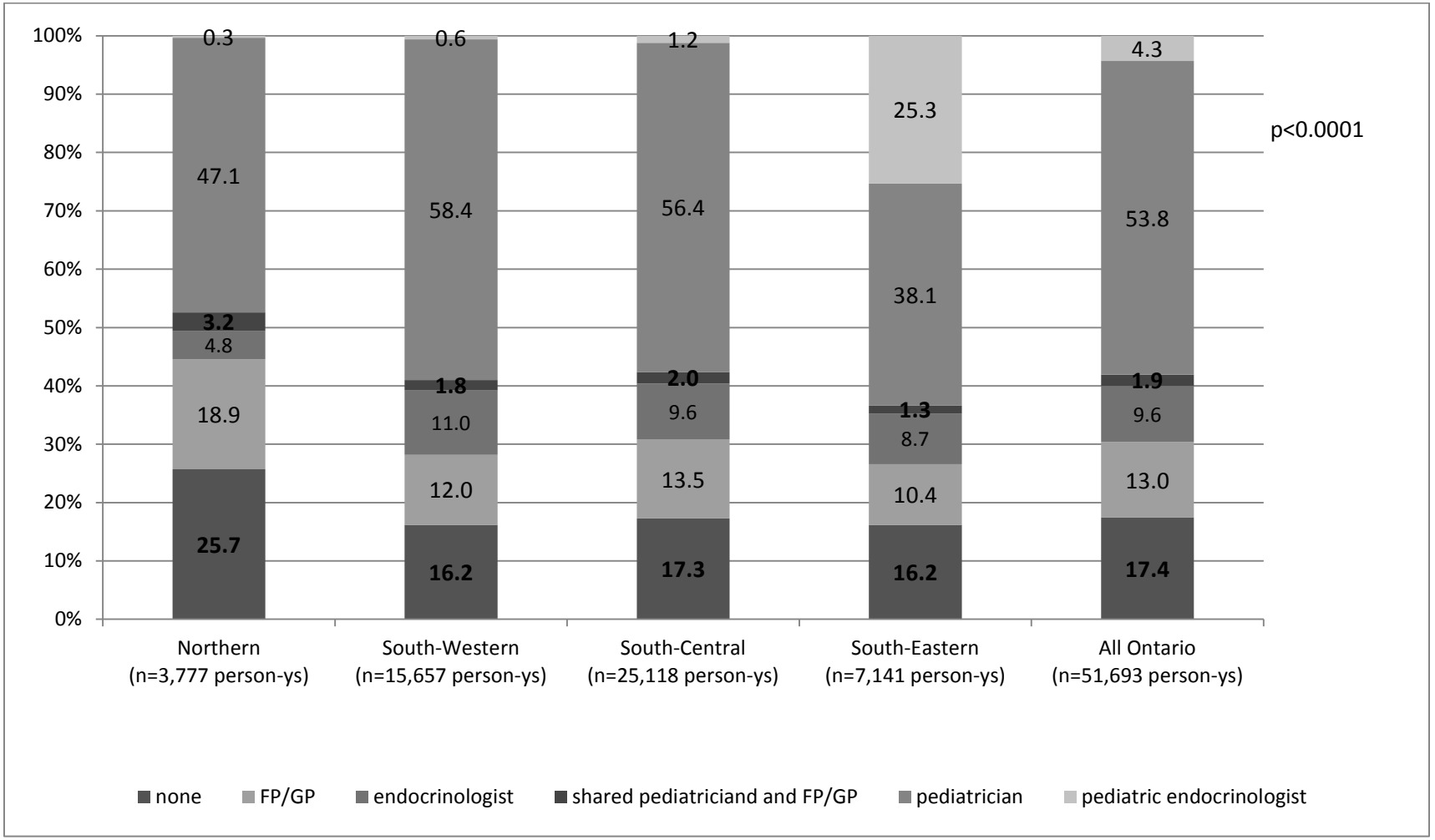

Figure 5-1: Main diabetes care physician providers of children with established diabetes by Ontario region in 2005-2014, % of observed person-years

Frequency of diabetes-related physician visits.

Near optimal frequency (3-5 visits/year) was observed in 46.8% of person-years (Table 5-3). In Northern Ontario this percentage was the lowest (35.1%) and, accordingly, the percentage of annual observations with below optimal number of diabetes-related physician visits (2 or less) was the highest (56% compared with 35.4-39.3% in other regions). Frequent visits were half as likely in Northern Ontario compared with South-Eastern Ontario (9% and 18%).

Diabetes management physician visits. In terms of physician visits claimed specifically as diabetes management care (fee codes K029, K030, K045 and Q040), South-Eastern Ontario had 30.6% of person-years with more than one DM visit compared with only 16.8% in Northern and Southern-Western Ontario and 8.5% in South-Central Ontario ($p< 0.0001$).

Diabetes-related ED visits. On average, 5.1% of all observed person-years had at least one record of diabetes-related ED visit. South-Western Ontario had significantly higher percentage of person-years with at least one diabetes-related ED visit (6.3%) in comparison to Northern Ontario (4.4%) and South-Central Ontario (4.3%) ($p<0 .0001$) (Table 5-3).

Psychiatrist consultations. Percentage of person-years with at least one visit to a psychiatrist also differed between regions (Table 5.4). On average, 1.9% of person-years in Northern Ontario had psychiatrist visits compared with 3.5% in all Ontario, 3.2% in South-Western Ontario, 3.8% in South-Central Ontario and 4% in South-Eastern Ontario ($p< 0.0001$).

Hospital admissions for DKA

The crude DKA hospital admission rate in the follow-up period was 3.6% (Table 5-4). The rate differed across Ontario regions: Northern and South-Western Ontario regions had the highest DKA hospital admission rate (3.9 and 4.2%, respectively) and South-Eastern Ontario had the

Table 5-3: Characteristics of diabetes-related physician visits by Ontario region

		Ontario region				
	Study cohort n=8687	Northern n=610	South-Western n=2589	South-Central n=4324	South-Eastern n=1164	Chi-square p-value
Total number of person-years	51,693	3777	15,657	25,118	7141	
Frequency of diabetes-related physicians visits, %	100.0	100.0	100.0	100.0	100.0	<0.0001
0-2 visits/year “below optimal”	39.1	56.0	39.3	37.4	35.4	
3-5 visits/year “near optimal”	46.8	35.1	47.4	48.3	46.5	
More than 5 visits “frequent”	14.1	9.0	13.3	14.3	18.1	
Frequency of diabetes management visits per person/year, %	100.0	100.0	100.0	100.0	100.0	<0.0001
None	70.2	68.1	66.6	77.8	52.8	
One	15.1	15.1	16.6	13.8	16.6	
More than one	14.6	16.8	16.8	8.5	30.6	
At least one diabetes related ED visit, %	5.1	4.4	6.3	4.3	5.4	<0.0001
At least one visit to a psychiatrist, %	3.5	1.9	3.2	3.8	4.0	<0.0001

lowest DKA hospital admission rate (2.7%). The lowest DKA hospital admission rate was observed in large urban areas (3.4%). Females were more likely to have DKA hospital admission than males (4.0 vs. 3.2%). Children residing in the most deprived areas (4.6%) and children who were diagnosed with diabetes at 7-12 years of age (4.3%) had the highest DKA hospital admission rate. DKA hospital admission rate more than doubled, from 2.2% in children in the least deprived neighbourhoods to 4.6% in the most deprived neighbourhoods (Table 5-4).

Table 5-5 shows DKA hospital admission rate by main diabetes care provider, diabetes-related physician and ED visits, presence of comorbidity and visits to a psychiatrist. DKA hospital admission rate differed by main diabetes care physician providers ($p< 0.0001$). The lowest DKA hospital admission rate (1.7%) was observed in person-years with no diabetes-related physician visits and with pediatric endocrinologist as the main provider (2.2%). The highest DKA hospital admission rate (5.1%) was associated with shared care involving both pediatricians and FP/GPs. DKA hospital admission was positively associated with frequency of diabetes-related physician visits in a preceding year (2.6% of children with 2 or less visits had DKA hospital admission compared with 6.6% of children with 6 or more visits). A similar pattern was observed for the number of DM visits: more frequent DM visits were associated with more frequent DKA hospital admission (Table 5-5). Children with at least one diabetes-related ED visit were almost four times more likely to have DKA hospital admission than children without any diabetes-related ED visits (11.5% versus 3.1%). Children with one or more comorbidity were two times more likely to have DKA hospital admission than those without comorbidities: 5.2% versus 2.5%. Children with at least one psychiatrist consultation were almost three fold more likely to have DKA hospital admission than those without psychiatrist consultations (9.1% versus 3.4%).

Table 5-4: DKA hospital admission crude rate by Ontario region and socio-demographic characteristics

	Total number of person-years	Person-years with at least one DKA	Crude DKA rate	*Chi-square p-value*
	N	n	n/N,%	
All study cohort (n=8687)	51,693	1842	3.6[a]	
Ontario region				*<0.0001*
Northern (n=610)	3777	148	3.9	
South-Western (n=2589)	15,657	657	4.2	
South-Central (n=4324)	25,118	844	3.4	
South-Eastern (n=1164)	7141	193	2.7	
Community[b]				*0.01*
Large urban (n-6743)	39,719	1365	3.4	
Urban (n=786)	5054	210	4.2	
Rural (n=1158)	6920	267	3.9	
Age group at diagnosis				*<0.0001*
0-6 (n=1905)	11,513	331	2.9	
7-12 (n=3265)	19,451	829	4.3	
13-18 (n=3517)	20,729	682	3.3	
Sex				*<0.0001*
Female (n=4144)	24,684	1045	4.0	
Male (n=4543)	27,009	913	3.2	
Deprivation index				*<0.0001*
1 (least deprived)(n=2246)	12,947	315	2.4	
2 (n=1945)	11,595	417	3.6	
3 (n=1693)	10,318	385	3.7	
4 (n=1305)	7865	323	4.1	
5 (most deprived)(n=1360)	8100	373	4.6	
Missing (n=138)	868	29	3.3	

Notes: [a]Annually, 3.6% or 1 in 28 children had at least one DKA hospitalization. [b]Defined using Statistics Canada Statistical Area Classification (SAC) codes: Large urban was defined as Census Metropolitan Areas (CMAs), with population 100,000 or greater, urban was defined as Census Agglomerations (CAs), with population 10,000-99,999; rural was defined as a community outside of CMAs or CAs, with population less than 10,000.

Table 5-5: DKA hospital admission crude rate by characteristics of physician visits and comorbidity

	Person-years, total number	Person-years with at least one DKA	Crude DKA rate	*Chi-square* p-value
	N	n	n/N, %	
All study cohort	51,693	1842	3.6	
Main diabetes care physician provider				*<0.0001*
No diabetes related physician visits	9000	149	1.7	
Pediatric endocrinologist	2205	48	2.2	
Endocrinologist	4948	185	3.7	
Pediatrician	27,831	1136	4.1	
FP/GP	6727	274	4.1	
Shared pediatrician and FP/GP	982	50	5.1	
Frequency of diabetes related physician visits				*<0.0001*
2 or less visits "minimal"	20,206	531	2.6	
3-5 visits "optimal"	24,192	832	3.4	
more than 5 visits "frequent"	7295	479	6.6	
Annual diabetes management visits				*<0.0001*
None	36,300	1,209	3.3	
One	7826	311	4.0	
More than one	7567	322	4.3	
At least one diabetes-related ED visit				*<0.0001*
Yes	2628	302	11.5	
No	49,065	1540	3.1	
Comorbidity (Charlson index)				*<0.0001*
None	31,854	802	2.5	
One or more	19,839	1040	5.2	
At least one visit to psychiatrist				*<0.0001*
Yes	1796	164	9.1	
No	49,897	1678	3.4	

Notes: FP/GP = family medicine/general practice; ED = emergency department.

Generalized linear mixed model (GLMM) of DKA hospital admission outcome

A series of generalized linear mixed models were fit to assess the effects of child's geographic region and use of physician diabetes care on the likelihood of DKA in each year of the follow-up period, adjusted for covariates, including geographic region and duration of diabetes; socio-demographic characteristics; characteristics of diabetes care in a preceding year; and, health status (Appendix VIII). We additionally ran the model 5 with all possible two-way interaction effects and included clinically meaningful and statistically significant interaction effects into the full model. The full model 5, which contained all ten variables and interaction effects between main diabetes care provider and comorbidity, and rural residence and psychiatrist visits, had the best model fit (Error variance=6.1 (0.71), $p<0.0001$, 2LogLikelihood=13479.3). Diabetes-related ED visits ($F=48.32$, $p< .0001$), comorbidity ($F=40.6$, $p<0.0001$) and at least one psychiatric consultation in the past year ($F=23.12$, $p<0.0001$) had the most significant effects on DKA hospital admission likelihood (Appendix VIII). The effect of child's geographic region on DKA hospital admission likelihood was statistically significant in models 2-4 ($p< 0.05$) until adjustment for comorbidity in the full model ($p=0.27$)(Appendix VIII). Community (rural or urban) did not have a significant effect on DKA hospital admission likelihood by itself ($p=0.62$); however, it interacted with psychiatrist consultations ($p=0.02$). There was also a statistically significant interaction effect of comorbidity and specialty of main diabetes care physician provider on DKA ($F=4.3$, $p= 0.0006$) (Appendix VIII).

Table 5-6 shows adjusted odds ratios (ORs) computed in the full model. The adjusted DKA hospital admission likelihood was 18-34% higher in all regions compared with South-Eastern Ontario region, but this difference was not statistically significant. DKA hospital admission was

1.1 times more likely to occur in rural communities than in larger urban. This difference also was not statistically significant (95% CI 0.87-1.45). The adjusted DKA hospital admission likelihood increased with each year since diagnosis at 4% (OR=1.04, 95% CI 1.01-1.06). Children who were diagnosed with diabetes at the age of 7-18 years were 34-48% more likely to have DKA hospital admission than children who were diagnosed at ages 0 to 6 years. Girls were 1.29 (95% CI 1.08-1.54) times more likely to have DKA hospital admission than boys. The effect of material deprivation on DKA hospital admission was increasing with increasing level of deprivation: children in the most deprived neighbourhoods were almost 2 times more likely to have DKA hospital admission than children in the least deprived neighbourhoods (OR=1.88 95% CI 1.42-2.5). Children who visited ED for diabetes reasons were almost two times more likely to have DKA hospital admission (OR=1.91, 95% CI 1.6-2.3). The effect of comorbidity was not significant for children who were cared by pediatric endocrinologists (OR=1.07 95% CI 0.47-2.45), but it was statistically significant for other diabetes care physician providers. The adjusted OR for children with comorbidities compared to children without comorbidity was 2.18 (95% CI 1.77-2.69) for those who were cared by pediatricians, 2.26 (95% CI 1.49-3.45) for children cared by endocrinologists, 3.8 (95% CI 2.62-5.51) for FP/GPs and 4.48 (95% CI 2.94-6.79) for those who did not have diabetes-related physician visits (Table 5-6).

Discussion

Previous studies on pediatric diabetes populations focussed on either diabetes care delivery (adherence to clinical practice guidelines, regular diabetes provider, frequency of diabetes visits, etc.) or health outcomes (DKA hospitalizations, all hospitalizations, ED visits). Our study is the first in the literature to analyze the relationship between physician services and health outcomes

Table 5-6: Adjusted odds of DKA hospital admission in Ontario children with established diabetes (generalized linear mixed modeling)

	OR Estimate	95% Confidence Interval	
Ontario region			
South-Central versus South-Eastern	1.18	0.87	1.60
Northern versus South-Eastern	1.20	0.78	1.82
South-Western versus South-Eastern	1.34	0.99	1.83
Community			
Urban versus large urban	1.01	0.76	1.34
Rural versus large urban	1.12	0.87	1.45
Urban versus large urban	0.90	0.64	1.26
Duration of diabetes, years	1.04	1.01	1.06
Age group at diagnosis			
13-18 versus 0-6	1.34	1.03	1.74
7-12 versus 0-6	1.48	1.17	1.88
Sex			
Girls versus Boys	1.29	1.08	1.54
Material deprivation quintile			
2 versus 1 (least deprived)	1.49	1.15	1.94
3 versus 1	1.52	1.16	2.00
4 versus 1	1.71	1.28	2.28
5 (most deprived) versus 1 (least deprived)	1.88	1.42	2.50
Interaction of Comorbidity (one or more versus none) and main diabetes care provider			
Pediatric endocrinologist	1.07	0.47	2.45
Shared pediatrician and FP/GP	1.52	0.75	3.07
Pediatrician	2.18	1.77	2.69
Endocrinologist	2.26	1.49	3.45
FP/GP	3.80	2.62	5.51
None	4.47	2.94	6.79
Number of diabetes physician visits			
“Frequent”(more than 5/year) versus “optimal”(3-5/year)	1.12	1.02	1.24
Had at least one ED visit for diabetes prior DKA			
Yes versus No	1.91	1.59	2.29
Had at least one psychiatrist visit prior DKA			
Yes versus No	2.27	1.61	3.22
Interaction of psychiatrist visit (yes versus no) and community			
Large urban	1.40	1.05	1.87
Urban	2.20	1.11	4.34
Rural	4.16	2.03	8.50

measured by acute diabetes complication (DKA) in a provincial pediatric population. In this study, we aimed to describe geographic differences in DKA hospital admission rates and characteristics of physician diabetes care for Ontario children with established diabetes and to understand the independent effects of geographic region and characteristics of diabetes-related physician visits on the likelihood of DKA hospital admission. On average, 3.6% or 1 in 28 in the cohort of Ontario children who were diagnosed with diabetes between2004 to 2012 and followed until March 31, 2015 were hospitalized for DKA annually. Our analyses showed that in Ontario the risk of DKA hospital admission in pediatric patients with diabetes varied across geographies. The lowest unadjusted DKA hospital admission rate was 2.7% (or 1 in 37) in South-Eastern Ontario compared with 3.4% (1 in 29) in South-Central Ontario, 3.9% (1 in 26) in Northern Ontario and 4.2% (1 in 24) in South-Western Ontario. Our statistical modeling showed that the effect of geographic region on the odds of DKA hospital admission persisted until we accounted for the effect of comorbidity, which had one of the strongest effects on DKA hospital admission in our study, along with visits to diabetes-related ED and psychiatrist visits in the year preceding DKA hospital admission. These factors indicate poorer health, their association with an increased risk of DKA hospital admission is well known in the literature.[38,56] Our study added evidence that the DKA hospital admission risk in children with diabetes and comorbidity may be decreased when they are cared by pediatric endocrinologists.

Indeed, our most important finding was that the effect of comorbidity on DKA hospital admission significantly varied depending on the child's main diabetes care physician provider. Thus, having one or more comorbidity did not increase odds of DKA hospital admission in children who were cared by pediatric endocrinologist (increase of 7% was not statistically

significant). However, patients with comorbidities who were cared by FP/GPs were almost 4 times more likely to have DKA hospital admission than patients without comorbidities. Patients with comorbidities cared by pediatricians were 2 times more likely to have DKA hospital admission than patients without comorbidities. The difference in the effect comorbidity on DKA hospital admission across physician specialties was not statistically significant; however, this finding has important clinical implications. It highlights the importance of clinical practice guidelines recommendation that all pediatric patients with diabetes have access to a pediatrician specialized in diabetes, preferably in endocrinology.[17,46,57-59] For example, absence of visits to endocrinologist within 120 days prior a DKA incidence was a strong predictor of the DKA hospital admission in pediatric patients with type 1 diabetes in California study.[56] Our finding showed that children with diabetes and comorbidities would benefit from subspecialist care the most, suggesting an important area for a targeted improvement of diabetes outcomes.

Our findings about the varying effect of comorbidity and physician specialist care on DKA hospital admission is in line with Ontario research on adult diabetic patients that reported that early endocrinologist care was associated with better health outcomes for medically complex patients while no benefit of specialist care was observed in non-medically complex patients.[24] Benefits of specialist care to children with comorbidities may be explained by previously reported better adherence to practice guidelines by pediatricians and pediatric endocrinologists than family physicians [23] and better metabolic control (measured by HbA1C) found in patients cared by pediatric endocrinologists. [60,61] Uneven benefits of physician specialist care may be related to how access to specialist care is organized overall. Kaiser et al.[62] compared diabetes

care delivery to low income pediatric patients in Ontario and California and found that significantly less Ontario children received routine diabetes care from pediatric endocrinologists than California children (27% vs. 64%). The authors suggested that this may be related to structural differences in how pediatric diabetes care is provided in California and Ontario. In Ontario, the OPDN supports FP/GPs in linking them to pediatric endocrinologists and multidisciplinary teams at tertiary centers. In California, most physician care is provided directly to the patients.

A fact that only 5 tertiary centers and 17 of 30 OPDN centers had pediatric endocrinologist (n=6) or visiting pediatric endocrinologist (n=11)[41] reflects uneven access to sub-specialist diabetes services and may explain variability of DKA hospital admission rates across the province. Indeed, South-Eastern Ontario had the lowest percentage of children with diabetes with comorbidities (23.5% compared with 37.8% in Ontario), who are known to have elevated risk of DKA, and the highest percentage of children seen by pediatric endocrinologists for diabetes care (25.3% compared with 4.3% for the entire province, less than 1% in Northern and South-Western Ontario). In contrast, Northern Ontario had the highest percentage of pediatric diabetic patients with comorbidities (more than half of all children with diabetes) and, yet, the lowest percentage of children receiving diabetes care from pediatric endocrinologists (0.3%) or pediatricians (47.1%). This mismatch between an increased need in comprehensive diabetes care due to prevalence of comorbidity and actual use of specialist diabetes care requires attention of Ontario health care decision makers. The existing literature suggests there are alternative ways of delivering effective diabetes care to pediatric patients in rural and northern areas where access to

specialists is limited, including outreach models with visiting pediatric diabetes specialists,[63-65] private care models[66] and use of telemedicine.[67-70]

Our analysis showed that children with mental problems (identified by visits to psychiatrist in our study) were 2.3 times more likely to have DKA hospital admission. This relationship is well established in the literature [38] and in practice[71] Our study adds to this body of literature the understanding of a differing effect of the mental problems on DKA for rural and urban children. Thus, rural children with psychiatrist visits prior DKA were 4.2 times more likely to have DKA hospital admission than rural children without psychiatrist visits. This effect was 2-3 times greater than one observed for children residing in urban areas. This finding may be explained by recent research showing that in Ontario, only 2 of 5 tertiary diabetes centers and none of 30 secondary pediatric diabetes centers had any full-time-equivalent psychologist and none of all 35 centers had a psychiatrist.[41] Similar to pediatric diabetes clinics around the world, [72,73] providing adequate mental health and psychosocial supports for pediatric diabetes patients and families is a major challenge in the OPDN.[71] Lack of access to a psychologist or psychiatrist care through the OPDN may have a stronger adverse effect on rural children than urban children, with urban children having potentially better access to other resources available in their communities to address their mental health care concerns, while rural children may have more limited access to such resources. Another Ontario study indicated an increasing geographic disparity in health outcomes between urban and rural children with diabetes.[42] Together, these findings indicate that urban-rural disparities in access to multidisciplinary pediatric diabetes care, including mental health care, represent important area of improvement of diabetes care and reduction of inequity for pediatric patients in Ontario.

Overall, the children in our study cohort received care that was below the level recommended by the international and national clinical practice guidelines.[46,57,74] For example, in less than 60% of all observed person-years care for pediatric patients was provided by pediatricians or pediatric endocrinologists; less than 50% of all observed person-years had 3 to 5 diabetes visits per year compared to quarterly visits recommended by the clinical guidelines; and, 70% of person-years had no recommended preventive diabetes management visits. Suboptimal adherence to clinical practice guidelines in care delivery in children with diabetes was also reported in British Columbia, where only 54% of person-years in pediatric population with T1D and less than 30% in pediatric population with T2D received recommended diabetes care.[22,23]

Similar to existing literature, our study found a direct relationship of adolescent age; [35,38] female sex;[37,38] duration of diabetes;[35] ED visits prior DKA hospital admission;[56] and material deprivation[75,76] with DKA hospital admission. Association of DKA hospital admission with female sex is usually attributed with poor weight control in girls[77] and a greater risk of developing eating disorders.[78] Duration of diabetes may contribute to DKA hospital admission due to "waning vigilance" in diabetes management as time passes from diagnosis.[22,23] ED visits for diabetes reasons may be an indicator of barriers to timely access to diabetes care and may be associated with undersupply of physicians and specialists in some areas.[79] Thus, in our study, South-Western Ontario had the highest ED visits compared to other Ontario regions and the highest DKA odds ratio. Similar to our findings, Nakhla et al. 2017 reported that, despite the implementation of the OPDN' decreased disparity in health outcomes based on income, Ontario

children from the most deprived neighbourhoods were still 2.11 (95% CI 1.77-2.52) times more at risk of hospitalizations compared with children from the least deprived neighbourhoods (compatible with the DKA hospital admission rate of 1.88 95% CI 1.42-2.5 in our study). [42]

The crude DKA hospital admission rate in our study (3.6%) was lower than similar DKA hospital admission rates reported in other developed countries by population-based studies of DKA hospital admission in children with established diabetes, including US (7.1%), Germany (5.0%), and UK (6.4%).[37] This difference may be due to the fact that our study included diabetes T1D and T2D combined, while other studies reported rates for children with T1D only who tend to be at higher risk of DKA due to insulin dependency. However, considering that about 90% of Ontario children with diabetes have T1D, we suggest that low DKA hospital admission rates in Canadian children with established diabetes may be attributed to the Canadian universal health insurance.

Children in our study, who used shared care (pediatrican and FP/GP) had the highest crude rate of DKA hospital admission (5.1%). This may be related to a period of transition to adult services, which is known to be a problematic time for youth with diabetes.[23,80] Interestingly, DKA hospital admission rates were lower in children with none diabetes-related physician visits. This finding may be associated with a good self-management of glycemic control and a decreased need in medical attention. However, for children who had one or more comorbidity, "below optimal" frequency of physician diabetes visits (less than 3/year) was associated with higher DKA rates. This indicates the importance of CPGs recommendation of quarterly diabetes visits for this subgroup of children with diabetes. We also found that children with frequent

(more than 5 visits/year) diabetes-related physician visits had the increased DKA hospital admission rate. This finding was in line with research indicating poor metabolic control in children with diabetes who had frequent, i.e., more than four diabetes clinic visits per year. [81-84] We agree that a plausible explanation of this relationship may be "an increased need for diabetes care to help manage blood glucose levels to the acceptable level."[85] Yet, reasons behind the increased need may be various, e.g., it can be comorbidity or a lack of diabetes self-management skills. Consequently, improvement of health outcomes would require different approaches in these cases.

There are several limitations of our study mostly related to the use of data that has been collected for administrative purposes and not intended originally for our study objectives. The data did not allow for distinguishing between type 1 and 2 diabetes nor were we able to account for clinical and familial factors known to be associated with DKA hospital admission, including glycemic control[35,47] and parental education level.[86] Our data was limited to claims from physicians and did not include non-physician diabetes care, provided by nurse practitioners, nurses, dietitians, social workers and other health care providers. Furthermore, data on physician services in the OHIP database may be incomplete because of a significant number of physicians who are part of family health groups or teams rather than on a fee-for-service model. These physicians claimed their services for administrative records ("shadow billings") rather than payment purposes, and thus may be under-reporting. Due to reliance on psychiatrist visits to identify children with mental health problems, our analysis did not include children receiving mental health care from other mental health care providers or those who had mental health problems undiagnosed or untreated.

Difficulties accessing health administrative data on certain populations (e.g., Indigenous, refugee and new immigrants to Canada) also pose limitations. We excluded 1,930 cases (18%) from the initial dataset, which had no physician diabetes-related claims in the entire follow-up period lasting from three to eleven years. A study by BC researchers encountered a similar situation with their study cohort based on health administrative data, where they excluded 12% of the initial pediatric diabetes cohort.[22] These cases may include children who received diabetes care from non-physician providers or covered by non-provincial funding (e.g., Indigenous children on reserve) that were not recorded in the OHIP database. Some degree of precision of our findings was lost due to the data source (ICES) privacy restrictions: we had to use grouping of child's age into 3 categories and 14 LHINs into four large geographic regions.

The strength of our study is due to the population-based longitudinal design and person-level data on DKA admissions linked with outpatient physician services claims, including ED visits. Longitudinal person-level data allowed us to observe DKA hospital admission incidence and use of physician services for each child in the study cohort up to eleven years post diagnosis. Statistical generalized linear mixed modeling allowed the generation of estimates of DKA hospital admission risk, accounting for multiple time points and covariates for each child. Our results complement those from other studies of Ontario children with established diabetes. We have added new knowledge by providing insights into the effects of geographic region and the use of physician services on DKA hospital admission. Future research is recommended to expand our understanding of pediatric diabetic care and DKA hospitalizations across a broader age range, and explore the impact of ethnicity, Indigenous status, and immigration status. Future

linkage with data on non-physician multidisciplinary outpatient diabetic services at the level of PDCs and LHINs may be helpful to guide policy and improve inequities in pediatric diabetic care and outcomes highlighted in our study.

Conclusions

Our study showed that DKA hospital admission rate in children with established diabetes residing in the province of Ontario were lower than in other developed countries; however, there were within-province inequities in pediatric DKA and use of physician specialist services based on geographic region. Policies aimed to improve health outcomes for children with established diabetes may consider improvements of access to pediatric endocrinologists, particularly for children with comorbidities, and access to mental health services, particularly for children with diabetes residing in rural areas

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Chapter 6

Discussion and Conclusions

The starting point of my thesis research was evidence of high pediatric DKA hospital admission rates in Northern Ontario in 1991-1999.[1,2] While it was possible this issue was primarily related to northern geography;[3] there may have been specific DKA risk factors contributing to this difference. For example, higher incidence of diabetes in the region may inflate DKA rates calculated for general population. On the other hand, because DKA is a condition preventable with proper diabetes management, the high DKA hospital admission rates may indicate insufficient access to quality diabetes care. There has been no research to date that examined what may be underlying high pediatric DKA hospital admission rates in the North. The purpose of my thesis was to address this gap in the literature by comparing Northern and Southern Ontario regions in terms of pediatric diabetes incidence (research question 1/paper 1), DKA hospital admission prevalence at the onset and throughout the course of diabetes (research question 2/paper 2 and 3) and physician diabetes care services used by children with established diabetes (research question 3/paper 3). I also aimed to explore another understudied topic, i.e., relationship between the use of health services for pediatric diabetes care and the occurrence of DKA hospital admission in children with established diabetes (research question 4/paper 3).

Available health administrative data determined the focus of my thesis on DKA episodes captured in hospital admissions (CIHI DAD data) and health services provided by physicians

(OHIP data). I employed Andersen's behavioural model of health services use (chapter 2.1) as my conceptual model. In the model (Figure 6-1), DKA hospital admission was the main health outcome and the two key concepts of interest were 1) geography conceptualized as external environment (four Ontario regions) and 2) children's use of physician diabetes care services. In the context of my conceptual model, the main objective of this study was to understand whether children's use of physician diabetes care services and geographic location of residence were independently associated with DKA hospital admissions, after considering predisposing characteristics (age group and sex), enabling resources (family's socio-economic status and rural or urban residence), and indicators of health needs (comorbidity and psychiatrist visits).

I used a population-based retrospective cohort research design and person-level linked health administrative data from the OHIP, CIHI-DAD and CIHI-NACRS databases to answer my research questions. In the following sections, first, I will discuss key findings from my papers (Chapters 3-5) organized in two themes: (I) preventive and risk factors of DKA hospital admissions identified in my study and (II) geography's effect on pediatric DKA hospital admissions, and how Northern Ontario compares to Southern Ontario regions in terms of pediatric DKA hospital admissions, diabetes incidence and patterns of children's use of physician diabetes care (Table 6-1). Next, I will consider how my study findings may inform improvements of health care access and outcomes for children with diabetes in Northern Ontario. I will conclude this chapter with outlining strengths and limitations of my study and directions for future research.

Table 6-1: Key study findings

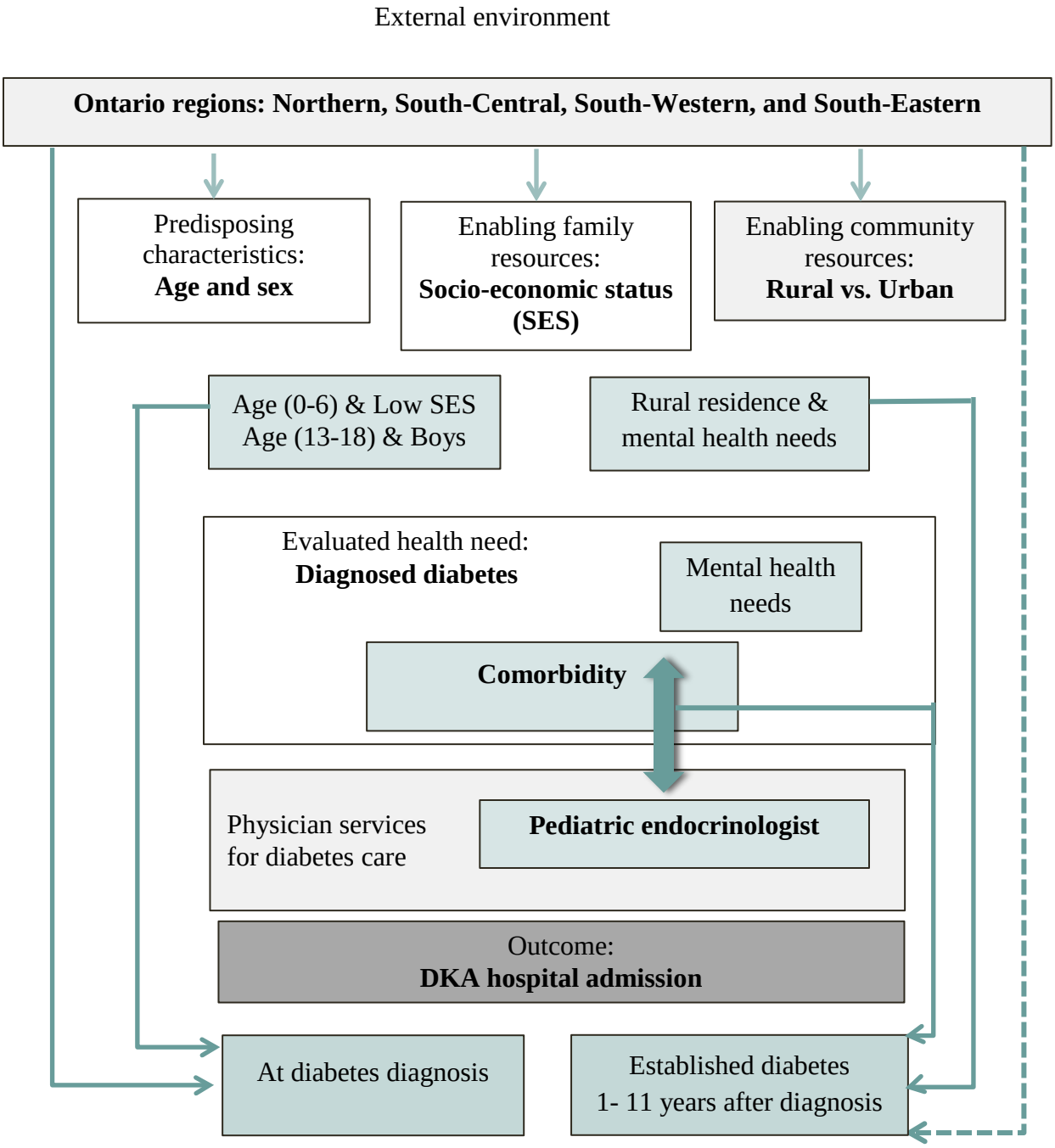
	Main focus	Relevance	New knowledge	So what? Implications
I.	Use of subspecialist diabetes care services.	Identified the effect of main physician provider of diabetes care on the likelihood of DKA hospital admission.	Diabetes care visits to pediatric endocrinologists reduced the risk of DKA hospital admissions, particularly for children with comorbidities. Children with comorbidities cared by FP/GP or those without main physician provider were at high risk of DKA hospital admission.	Children with diabetes and comorbidities should be cared by a pediatric endocrinologist.
	Risk factors of DKA hospital admissions.	Identified age-specific risk factors of DKA hospital admission at diabetes diagnosis (paper 2).	Younger children (0-6 years) in the most deprived neighbourhoods and adolescent boys were at high risk of DKA hospital admission at diabetes diagnosis.	Informs targeted prevention of DKA.
		Identified the interactive effect of rural residence and mental health needs on the likelihood of DKA in children with established diabetes (paper 3).	Rural children with mental health needs were at higher risk of DKA hospital admission than urban children with mental health needs.	Informs targeted prevention of DKA.
II	Effects of geography on DKA hospital admissions.	The first study on Ontario children with diabetes that considered variation across Ontario geographic regions, based on LHINs.	South-Eastern Ontario had the lowest prevalence of DKA hospital admissions in children with established diabetes and South-Western had the highest prevalence of DKA hospital admissions.	There is room for improvement of pediatric diabetes care and health outcomes at the regional level.

Main focus	Relevance	New knowledge	So what? Implications
Northern Ontario in comparison to Southern Ontario regions.	The first study on Northern Ontario children with diabetes (papers 1-3).	In Northern Ontario, children with diabetes were sicker and from poorer families. Lower percentage of children visiting pediatric endocrinologists and pediatricians. Higher proportion of children without main physician diabetes care provider and higher prevalence of DKA hospital admissions in the course of diabetes.	May inform policies and programs aimed to improve access to quality health care for children with diabetes in Northern Ontario.
	The first update of provincial pediatric diabetes incidence since 1991-99 (ICES, Diabetes in Ontario, 2003)(paper 1).	Northern Ontario had the highest incidence of pediatric diabetes in the province.	Background statistics on diabetes incidence may inform prevention and management of diabetes.
	The first update of DKA hospital admission rates at diabetes diagnosis since 1994-2000 (paper 2).	Northern Ontario had the lowest prevalence of DKA hospital admissions at diabetes diagnosis.	May inform programs on prevention of DKA and reduction of health care costs associated with DKA hospital admissions.
	The first study on DKA hospital admissions in children with established diabetes in Ontario (paper 3).	Northern Ontario had the highest prevalence of DKA hospital admissions in children with established diabetes.	

6.1. Protective and risk factors of DKA hospital admissions

Understanding protective and risk factors of DKA is important for targeted prevention of this acute complication and improvement of health outcomes for children with diabetes. Below, I will discuss DKA factors that were found to be significant in my study, i.e., access to subspecialist care; age and material deprivation; age and sex; and, rurality and mental health needs. Figure 6-1 shows groups of children with diabetes who were at high risk of DKA hospital admission (green shaded boxes).

Access to subspecialist care. International and national CPGs for pediatric diabetes care recommend that children receive care from pediatric specialists (subspecialists); however, there has been limited evidence of the effect of subspecialist care on health outcomes.[4,5] Paper 3 in my thesis contributed to this literature by demonstrating that seeing a pediatric endocrinologist as the main diabetes care provider reduced the likelihood of DKA hospital admission for a child with diabetes in Ontario, particularly, for a child with diabetes and comorbidities. At the same time, having comorbidity increased the risk of DKA hospital admission for a child with diabetes, who saw only an FP/GP, FP/GP and pediatrician, or did not have any diabetes related physician visits. This finding strongly suggests that children with diabetes and comorbidities must be seen by a pediatric endocrinologist for routine diabetes care to prevent diabetes complications. It complements previous research that reported better adherence to the CPGs by pediatric specialists[6] and improved glycemic control associated with subspecialist care in children with diabetes.[4,5] It is important to acknowledge, however, that comprehensiveness of subspecialist care is not determined by physician's specialty, but also by the context of subspecialist care. That



Note: Green shaded boxes and bold arrows indicate DKA hospital admission factors identified in my study. Dashed arrow indicates the effect of geography on DKA hospital admissions in children with established diabetes.

Figure 6-1: DKA hospital admission factors

is to say, subspecialist care is usually provided in academic tertiary hospitals with access to advanced interdisciplinary, diagnostic and laboratory technology support that may not be available for FP/GPs in community settings. Future research that considers these aspects of pediatric diabetes care (e.g., psychosocial support, clinical tests, dietary education, and so on) that are not captured in health administrative data may provide better understanding of the effect of processes of pediatric diabetes care on DKA and other health outcomes for children with diabetes.

Youngest children (0-6 years) in the most deprived areas were at increased risk of DKA hospital admission at diabetes diagnosis. Previous literature indicated that both age and material deprivation are independently associated with the risk of DKA at diabetes diagnosis. In my study cohort of Ontario children diagnosed with diabetes in 2004-2012, material deprivation was a significant risk factor of DKA hospital admission at diabetes diagnosis only among children in younger age (0-6 years). In this age group, children in the most deprived areas were more likely to be diagnosed with diabetes during hospitalization for DKA than children in the least deprived areas. Considering that some studies reported a significant decrease in DKA frequency after education campaign, this finding suggests a need for increasing awareness about diabetes symptoms in young children among parents and physicians, particularly those living and working in the most deprived neighbourhoods.

Adolescent boys were at increased risk of DKA hospital admission at diabetes diagnosis. Another age-specific group in my study cohort at high risk of DKA at diabetes diagnosis were 13-18 year boys. As indicated in paper 2, this may be due to difference in behavioural patterns of

primary care use by adolescents, with boys being less frequent users of physician services than girls. Targeting health promotion through the diabetes education and school system is one possible direction for improvement of health and health behaviour of adolescents.[7,8]

Rural children with mental health problems were at increased risk of DKA hospital admission in the course of diabetes. One of the important findings of my thesis was related to DKA outcomes for children residing in rural communities. On one hand, my study showed that DKA hospital admissions at diabetes diagnosis were not associated with the child's rural residence. This is an encouraging finding that may be explained by universal access to health care available for all Ontario children regardless of residence. On the other hand, in the course of diabetes, risk of DKA hospital admission was significantly higher for children with mental health needs residing in rural communities than those residing in urban communities. Provision of adequate mental health and psychological supports for children with diabetes is a major challenge across Ontario[9] and in other Canadian jurisdictions.[10] My study indicates, however, that having mental health needs had a triple adverse effect on health of rural children than urban children with diabetes. This finding has an important implication for a targeted improvement of access to mental health care for rural children with diabetes.

6.2. DKA hospital admissions in Ontario children with diabetes: geography matters.

My study provided evidence of that geography or where a child with diabetes lives in Ontario matters in terms of the risk of acute complication such as DKA. Overall, my analyses showed that in 2004-2012, the largest regional difference in DKA hospital admission rates was 1.3-fold

at diabetes diagnosis between South-Western Ontario and Northern Ontario and 1.6-fold in children with established diabetes (1.3-fold after accounting for socio-demographics, comorbidity and use of physician diabetes services) between South-Western and South-Eastern Ontario. Not all of the observed geographic differences were statistically significant; however, they all are clinically important as DKA is a serious diabetes complication associated with high morbidity and mortality. It is important to note that the true extent of geographic variability of DKA hospital admission rates may be underestimated in my study due to aggregation of 14 Ontario LHINs over four large geographic regions.[11] Future research at the single LHIN level is warranted as it may reveal higher geographic variations in DKA hospital admissions across the province. Such research will provide health care decision makers with more knowledge for informed decisions (e.g., allocation of funds and resources) aligned with varying health needs of children with diabetes in different regions.

Geographic variation of children's use of diabetes care services found in my study may be related to the variation in local physician supply reported across the province[12] and variability in access to specialised care and other resources across 35 PDCs where 90% of Ontario children receive diabetes care.[13] These differences indicate that there is room for improvement of health care and outcomes for children with diabetes in the province and that DKA prevention strategies are needed, particularly in areas with the highest DKA rates, including South-Western and Northern Ontario.

6.2.1. Children with diabetes in Northern Ontario

During the nine-year period from 2004 to 2012, Northern Ontario had the highest pediatric diabetes incidence in the province with the age-and-sex standardized rate of 46.4/100,000 (Table 3-3). The rate was 22% higher than in South-Central Ontario, 13% higher than in South-Eastern and 9% higher than in South-Western Ontario (Table 3-4). Prevalence of DKA hospital admissions at diabetes diagnosis was the lowest in Northern Ontario (13.1%) (versus the highest of 17.2% in South-Western Ontario)(Table 4-3). This difference may be related to a larger proportion of children with T2D in Northern Ontario than in other regions (31% versus 4%).[14] Children with T2D are known to be at lower risk of DKA at the onset of diabetes than children with T1D.[15] In children with established diabetes, crude prevalence of DKA hospital admissions was higher in Northern Ontario than in Southern regions of Ontario, particularly in South-Eastern Ontario (3.9% versus 2.7% per year)(Table 5-4).

As discussed in paper 3, the DKA hospital admission rate in the North was associated with children's population characteristics and use of physician services for diabetes care. First, compared with Southern Ontario, children in Northern Ontario were more likely to be diagnosed with diabetes later in childhood (at the age of 13-18), have comorbidities at the time of initial presentation, or live in poorer neighbourhoods. These population characteristics are known to be risk factors of DKA. Next, my study indicated that having a pediatric endocrinologist as the main diabetes care provider had a substantial preventive effect against DKA hospital admission in the course of diabetes, particularly in children with comorbidities. However, in Northern Ontario, where a significant proportion of children with diabetes have comorbidities (54%)(Table 5-2), only 0.3% of all person-years had seen pediatric endocrinologists (Figure 5-1). For comparison,

in South-Eastern Ontario, 23% of all children with diabetes had one or more comorbidity (Table 5.3) and 25% of all children with diabetes received diabetes care from a pediatric endocrinologist (Figure 5-1). Furthermore, Northern Ontario children with diabetes had the lowest proportion of those who used psychiatrist physician services. This was more likely due to the limited access to psychiatrists in the North[16] rather than lower mental health needs in northern children with diabetes. In my study cohort, children with diabetes and mental health needs residing in rural communities were at higher risk of DKA hospital admission than those residing in urban communities. In light of this finding, the fact that almost 40% of Northern Ontario children with diabetes lived in rural communities (Table 5-2) represented an additional DKA risk burden for Northern Ontario children and may be contributed to high DKA hospital admission rate in the North.

Finally, my study showed that the proportion of children who were without a main diabetes care physician provider was 25.7% in the North compared to 16-17% in other regions (Figure 5-1). Similarly, the proportion of children who had the "below optimal" (less than 3) number of physician visits was higher in the North compared to the South (56% versus 35-39%)(Table 5-4). This difference may be explained by an overall shortage of physicians in Northern Ontario communities,[17] lack of subspecialists and long distances to the closest multidisciplinary diabetes clinic in Ontario (on average, 100 km to secondary PDCs and 350 km to tertiary PDCs).[9] For Northern Ontario families with children with diabetes, trips to access specialist diabetes care may include costs of transportation, meals, accommodation, lost time from work and wages, and additional daycare expenses for other children. The Ontario's Northern Health Travel Grant

covers some part of the transportation and accommodation, but not the full travel cost that may be difficult or even impossible to afford for some households.

Overall, Northern Ontario children with established diabetes were at higher risk of DKA hospital admission compared with children in South-Central and South-Eastern regions. Predisposing socio-demographic characteristics, comorbidities and suboptimal use of physician services for diabetes care may explain the increased prevalence of DKA hospital admissions in the Northern region. At the same time, in South-Eastern Ontario (home of a world leader in pediatric health, the Children's Hospital of Eastern Ontario/CHEO), [18] patterns of pediatric physician diabetes care were the best in the province (e.g., 25% of children with diabetes had a pediatric endocrinologist as the main diabetes care physician provider)(Figure 5-1). As well, prevalence of DKA hospital admissions in children with established diabetes was the lowest in the province (2.7% per person/year)(Table 5-4).

The comparison between Northern Ontario ("poor" characteristics of pediatric diabetes care and DKA outcomes) and South-Eastern-Ontario ("best" pediatric diabetes care and DKA outcomes) provides evidence of the relationship between physician diabetes care and DKA not only at the individual level (based on the multivariate analyses from paper 3); but also at the regional level (pointing out to systemic barriers to health care access). This contrasting evidence suggests a need for improvement of access to quality pediatric diabetes care in Northern Ontario. In the next section, I will discuss opportunities for the improvement in light of the current provincial health policy priorities.

6.3. Knowledge translation

My thesis findings are consistent with recently published Ontario research on delivery of pediatric diabetes care in the province through the pediatric diabetes network;[9] health care and outcomes for Ontario children with diabetes from low-income families in 2009-2012;[13]and time-trends in pediatric diabetes related ED visits and hospital admissions in 1996-2011.[19] These studies indicated an overall improvement of pediatric diabetes care and outcomes in Ontario since implementation of the OPDN in 2001; however, they also found persisting disparities in the use of specialised diabetes care (e.g., insulin pumps, multidisciplinary and subspecalist care) and outcomes (ED visits and hospital admissions for diabetes complications) based on income[13] or place of residence (rural or urban).[19] In agreement with these studies, my research indicated disparities in the risk of DKA hospital admission based on material deprivation, rurality and geography with most deprived, rural and northern children being at higher risk of the acute diabetes complication. These research findings together provide strong evidence for the need of improvement of access to pediatric diabetes care and reduction of inequities in health outcomes for children in Ontario, and, particularly, in Northern Ontario.

Concerns about health inequity in rural and northern Ontario have been long standing.[20,21] Thus, my study's findings about insufficient access to subspecialist care and higher risk of acute diabetes complication among Northern Ontario children with diabetes are not unexpected. Implications of the findings align well with the Northern Strategy for Health Equity ("Northern Strategy"),[22] commissioned by the previous provincial liberal governement. If successful, the Northern Strategy may improve health care and outcomes for children with diabetes in the region.

One of the four Northern Strategy's foundations is achievement of "equitable access to high-quality and appropriate health care services" for Northerners. This includes improvements in recruitment and retention of health care professionals; assessment and expansion of the Ontario Telemedicine Network (OTN); improvement of transportation, especially to major health hubs from outlying areas; and informed policy changes to the Northern Health Travel Grant to meet the needs of people living with low-income. These measures would definitely benefit children with diabetes. Furthermore, Northern Ontario children with diabetes may directly benefit from the Northern Strategy's priority for diabetes prevention and managament in the region. However, achievement of health equity requires an approach that acknowledges varying needs of different people and populations. Thus, within this priority, it is important to realize that health care needs of children with diabetes are different from those of adults with diabetes and must be tackled with the input by pediatric experts.[23] Moreover, there is evidence that disadvantage in access to health care has a larger adverse impact on health of children and youth than adults.[24,25] Thus, I suggest that it is imperative that the Northern Strategy implements measures with consideration of specific needs of pediatric diabetes population in the region.

Availability of strong evidence for decision makers is another important foundation of the Northern Strategy for Health Equity. For knowledge translation, I intend to prepare a presentation based on my thesis results to the Northern Network for Health Equity, North East and North West LHINs, and Public Health Sudbury&Districts. I will also submit a summary of findings to the Ministry of Health and Long Term Care, Provincial Council of Maternal and Child Health, and the OPDN. Knowledge about most vulnerable subgroups of children with diabetes (young children in low income families, adolescent boys, and rural children with mental

health needs) may inform a targeted approach to reduce health inequity in the North. The evidence of preventive effect of access to pediatric endocrinologists, particularly for children with diabetes and comrobidities, may inform actions to improve the use of telemedicine[26] or other outreach pediatric diabetes care models for rural children with diabetes.[27,28] Children`s use of subspecialist care and DKA hospital admission rates may be used as indicators to measure progress on achieving quality and equity of diabetes care in Northern Ontario and other Ontario LHINs down the road.

6.4. Strengths and limitations

In terms of the conceptual framework (Figure 6-1), my thesis extended the knowledge on health outcomes for Ontario children with diabetes by adding into consideration: geographic regions based on Ontario LHINs through which the provision of pediatric diabetes care is funded and managed (external enviornment); indicators of health needs of children with diabetes including mental health needs and comorbidity; use of physician diabetes care services, including physician speciality of main diabetes care provider and frequency of diabetes visits; and timing of health outcomes (DKA hospital admission at the time of diabetes diagnosis and in the course of diabetes). Consideration of these concepts in my analyses allowed capturing the complexity of DKA factors and observing regional variation in DKA hospital admissions and physician care services use in Ontario children with diabetes.

This study is the first (to the best of my knowledge) to analyze the relationship between the use of physician services and DKA hospital admission as an indicator of health outcomes for the population of children with diabetes in Ontario. It contributes to the evidence of the significant positive effect of subspecialist care on health outcomes for pediatric patients with diabetes.[4,29,30]

The strength of the study stems from the use of population-based retrospective cohort (longitudinal) research design and person-level linked data. This combination allows avoiding ecological fallacy by complementing the study of pediatric DKA hospital admissions at the regional level with assessing the likelihood of pediatric DKA hospital admissions at the individual level.

This study has limitations related to the secondary use of health administrative data that were collected for administrative purposes and not intended originally for my study objectives. The available health administrative data lacks information on glycemic control and direct measures of socio-economic status. Difficulties accessing data on certain populations (e.g., Indigenous, refugee and new immigrants to Canada) and services (e.g., non-physician diabetes care provided by nurses, dietitians and other providers in multidisciplinary diabetes clinics) also pose limitations. Using OHIP physician billing data may underestimate the utilization of physician services for pediatric diabetes care because of lack of information on services by physicians who are not on fee-for-service payments or because of incomplete shadow billing.

The pediatric diabetes case identification algorithm in my study did not distinguish between T1D and T2D, which may be associated with differing patterns of incidence, physician services use and acute diabetes complications (such as DKA). Future research distinguishing between the two types of diabetes may provide a more nuanced understanding of incidence of diabetes and DKA, as well as utilization of diabetes care and health outcomes for Ontario children with diabetes (as has been done in British Columbia).[6,31-33] Future research at the single LHIN level is warranted as it may reveal higher geographic variations in DKA hospital admissions across the province.

Such research will provide health care decision makers with more detailed knowledge for informed decisions (e.g., allocation of funds and resources) aligned with varying health needs of children with diabetes in different regions.

Concluding remarks

From a public policy perspective, investing in the health of children is as essential to the national growth as investing in infrastructure.[34] Every dollar invested during childhood is estimated to be worth 3 to 18 health care dollars later in life.[35] This is especially true for children with diabetes, whose health is compromised by the chronic disease, which makes them susceptible to life-long consequences and complications, with the risks magnified by the early onset of the disease.[36-40] Considering long-lasting effects of DKA on child's health and excessive health care costs associated with treatment of this acute complication in the hospital setting, my study findings have implications for targeted prevention of DKA, health policy ensuring equitable access to diabetes care across the province and minimizing avoidable health care costs, and, ultimately, for health of children with diabetes in Ontario.

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APPENDIX I

Laurentian University Research Ethics Board certificates

APPROVAL FOR CONDUCTING RESEARCH INVOLVING HUMAN SUBJECTS

Research Ethics Board – Laurentian University

This letter confirms that the research project identified below has successfully passed the ethics review by the Laurentian University Research Ethics Board (REB). Your ethics approval date, other milestone dates, and any special conditions for your project are indicated below.

TYPE OF APPROVAL / New **X** / Modifications to project / Time extension

Name of Principal Investigator and school/department	Oxana Mian, CRaNHR, supervisor, Elizabeth Wenghofer, CRaNHR & NOSM
Title of Project	Hospitalizations for diabetic ketoacidosis (DKA) in children with diabetes in northern and southern Ontario: assessing time trends and relationship with physician visits using health administrative data
REB file number	2016-04-02
Date of original approval of project	April 22, 2016
Date of approval of project modifications or extension *(if applicable)*	
Final/Interim report due on: *(You may request an extension)*	April 22, 2017
Conditions placed on project	

During the course of your research, no deviations from, or changes to, the protocol, recruitment or consent forms may be initiated without prior written approval from the REB. If you wish to modify your research project, please refer to the Research Ethics website to complete the appropriate REB form.

All projects must submit a report to REB at least once per year. If involvement with human participants continues for longer than one year (e.g. you have not completed the objectives of the study and have not yet terminated contact with the participants, except for feedback of final results to participants), you must request an extension using the appropriate LU REB form. In all cases, please ensure that your research complies with Tri-Council Policy Statement (TCPS). Also please quote your REB file number on all future correspondence with the REB office.

Congratulations and best wishes in conducting your research.

Rosanna Langer, PHD, Chair, *Laurentian University Research Ethics Board*

APPROVAL FOR CONDUCTING RESEARCH INVOLVING HUMAN SUBJECTS

Research Ethics Board – Laurentian University

This letter confirms that the research project identified below has successfully passed the ethics review by the Laurentian University Research Ethics Board (REB). Your ethics approval date, other milestone dates, and any special conditions for your project are indicated below.

TYPE OF APPROVAL / New / Modifications to project **X** / Time extension

Name of Principal Investigator and school/department	Oxana Mian, CRaNHR, supervisor, Elizabeth Wenghofer, CRaNHR & NOSM
Title of Project	Hospitalizations for diabetic ketoacidosis (DKA) in children with diabetes in northern and southern Ontario: assessing time trends and relationship with physician visits using health administrative data
REB file number	2016-04-02
Date of original approval of project	April 22, 2016
Date of approval of project modifications or extension *(if applicable)*	June 22, 2016
Final/Interim report due on: *(You may request an extension)*	April 22, 2017
Conditions placed on project	**ICES Confirmation of Feasibility, June 14, 2016 provided by researcher**

During the course of your research, no deviations from, or changes to, the protocol, recruitment or consent forms may be initiated without prior written approval from the REB. If you wish to modify your research project, please refer to the Research Ethics website to complete the appropriate REB form.

All projects must submit a report to REB at least once per year. If involvement with human participants continues for longer than one year (e.g. you have not completed the objectives of the study and have not yet terminated contact with the participants, except for feedback of final results to participants), you must request an extension using the appropriate LU REB form. In all cases, please ensure that your research complies with Tri-Council Policy Statement (TCPS). Also please quote your REB file number on all future correspondence with the REB office.

Congratulations and best wishes in conducting your research.

Rosanna Langer, PHD, Chair, *Laurentian University Research Ethics Board*

APPROVAL FOR CONDUCTING RESEARCH INVOLVING HUMAN SUBJECTS

Research Ethics Board – Laurentian University

This letter confirms that the research project identified below has successfully passed the ethics review by the Laurentian University Research Ethics Board (REB). Your ethics approval date, other milestone dates, and any special conditions for your project are indicated below.

TYPE OF APPROVAL / New / Modifications to project / Time extension **X**

Name of Principal Investigator and school/department	Oxana Mian, CRaNHR, supervisor, Elizabeth Wenghofer, CRaNHR & NOSM
Title of Project	Hospitalizations for diabetic ketoacidosis (DKA) in children with diabetes in northern and southern Ontario: assessing time trends and relationship with physician visits using health administrative data
REB file number	**6009778** (former file no. 2016-04-02)
Date of original approval of project	April 22, 2016
Date of approval of project modifications or extension *(if applicable)*	June 22, 2016 April 25, 2017
Final/Interim report due on: *(You may request an extension)*	April 22, 2018
Conditions placed on project	

During the course of your research, no deviations from, or changes to, the protocol, recruitment or consent forms may be initiated without prior written approval from the REB. If you wish to modify your research project, please refer to the Research Ethics website to complete the appropriate REB form.

All projects must submit a report to REB at least once per year. If involvement with human participants continues for longer than one year (e.g. you have not completed the objectives of the study and have not yet terminated contact with the participants, except for feedback of final results to participants), you must request an extension using the appropriate LU REB form. In all cases, please ensure that your research complies with Tri-Council Policy Statement (TCPS). Also please quote your REB file number on all future correspondence with the REB office.

Congratulations and best wishes in conducting your research.

Rosanna Langer, PHD, Chair, *Laurentian University Research Ethics Board*

APPENDIX II

Permission to reproduce Andersen's model of health services use

APPENDIX III

Table: Variables and definitions

N	Variable	Source	Definition
1	ID	ODD	Encrypted health card number
2	Cohort	ODD	1-9 (based on the year of diagnosis)
3	Year of diagnosis	ODD	2004-2012
4	Age group at diagnosis	ODD	0-6; 7-12; 13-18 years old
5	Sex	ODD	Male, female
	DKA hospital admission	CIHI-DAD	Code E10.0-10.12 (ICD-10CA).
6	Admission date	CIHI-DAD	Number of days post diabetes diagnosis
7	Patient's geography	CIHI-DAD	LHIN (1-14)
8	Patient's rurality	CIHI-DAD	SAC code (1-7)
	Physician claims:	OHIP	All physician claims of services
9	Service date	OHIP	Number of days post diabetes diagnosis
10	Fee code	OHIP	Ministry of Health *Schedule of Benefits, Physician Services under the Health Insurance Act* (October 1, 2013).

N	Variable	Source	Definition
11	Diagnostic code	OHIP	250 (diabetes and complications) Other codes
12-15	Physician provider Information	OHIP	Specialty, LHIN, rural/urban, SAC code
	Emergency department visits:	CIHI-NACRS	Unplanned emergency visits, exclude day surgeries or clinics taking place in the ED.
16	Visit date	CIHI-NACRS	Number of days post diabetes diagnosis
17	Triage level	CIHI-NACRS	Case severity assigned in the ED
18	Visit disposition	CIHI-NACRS	Identifies whether the patient was admitted, transferred, discharged home, etc.
19	Main problem	CIHI-NACRS	The problem the patient presents with that is clinically significant (ICD-10-CA diagnosis code)
20	Proxy for socio-economic status	ON-Marg	ON-Marg quintile (1-5) at diabetes diagnosis
21	Comorbidity	Charlson index	0=none, 1=one; 3=more than one

Notes: ODD = Ontario Diabetes Database; OHIP = Ontario Health Insurance Plan; CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database; CIHI-NACRS = Canadian Institute for Health Information National Ambulatory Care Reporting System; SAC = Statistics Canada Area Classification; ON-Marg = Ontario Marginalization Index

APPENDIX IV

Table: Diabetes incidence among Canadian children and youth: a summary of published studies

Region/Author/Pub year/Journal	Time period	Data source/ Population	N of cases/ Age range	Diabetes type[a]	Incidence rate per 100,000/year
Canada					
Amed et al. (2010) *Diabetes Care*	2006-2008	Survey of pediatricians, pediatric and adult endocrinologists, family practitioners.	345 0-19	T2D	1.54 (All) 23.2 (Indigenous), 0.54 (Caucasian) 7.7 (Asian), 1.9 (African/Caribbean)
Ontario					
Ehrlich et al. (1982) *Diabetologia*	1976-1978	Hospital records Toronto Metropolitan	132 0-18	T1D	9.0
Bui et al. (2010) *J Pediatr*	1994-2000	Provincial health administrative data All Ontario	3947 0-18	T1D &T2D combined	29.7
To et al. (2003) *ICES Diabetes Atlas*	1996-2000	Provincial diabetes registry data All Ontario	Number not reported 0-19	T1D &T2D combined	27.1 23.9 in 1996 28.0 in 2000
Guttmann et al. (2010) *Pediatr Diabetes*	1994-2003	Provincial health administrative data All Ontario	5591 0-19	T1D &T2D combined	28.0 24.5 in 1994 32.3 in 2003

Region/Author/Pub year/Journal	Time period	Data source/ Population	N of cases/ Age range	Diabetes type[a]	Incidence rate per 100,000/year
Manitoba					
Blanchard et al. (1997) *Diabetes Care*	1985-1993	Manitoba Diabetes Database	434 0-14 years	T1D	20.4
Sellers et al. (2012) *Can J Diabetes*	2006-2011	Diabetes Education Resource for Children and Adolescents, Winnipeg	227 0-18	T2D	20.6 in 2011
Quebec					
Legault et al. (2006) *Clin Invest Med*	1989-2000	Provincial government database	n=240/year ~2880 0-18	T1D	15.0
Alberta					
Toth et al. (1997) *Diabetes Care*	1990-1995 Edmonton	Provincial health administrative data	n=211 0-14	T1D	25.7
Oster et al. (2012) *Int J Circumpolar Health*	1995-2007 Aboriginal	Provincial health administrative data	n=2589 <20 years	T1D &T2D combined	22 in 1995 59 in 2007 (crude rates)

Region/Author/Pub year/Journal	Time period	Data source/ Population	N of cases/ Age range	Diabetes type[a]	Incidence rate per 100,000/year
Newfoundland and Labrador					
Newhook et al. (2004) *Diabetes Care*	1987-2002	A pediatric diabetes treatment centre	294 0-14	T1D	36
Newhook et al. (2008) *Pediatr Diabetes*	1987-2005	Diabetic nurse educators registries; hospital medical records; provincial diabetes camp registry.	732 0-14	T1D	35
Newhook et al. (2012) *BMC Res notes*	1987-2010	Diabetic nurse educators registries.	931 0-14	T1D	38 in 1987-2010 50 in 2007-2010
British Columbia					
Amed, et al. (2013) *Status report*	1998/99-2006/07	Provincial health administrative data	4019 0-19	T1D and T2D	32.5 in 2007 26 (T1D) 2007 5.5 (T2D) 2007
Fox, et al. (2017) *Pediatr Diabetes*	2002/03-2012/13	Provincial health administrative data	201-250/year 0-19	T1D	23 in 2002/03 27 in 2012/13
Amed et al. (2018) *Pediatr Diabetes*	2002/03-2012/13	Provincial health administrative data	0-19	T2D	5.2 in 2012

Notes: T1D=Type 1 diabetes, T2D=Type 2 diabetes.

APPENDIX V

Table: Diabetes incidence rates and annual percent change by age group, sex, and year period[a]

	Diabetes incidence rates by year period, per 100,000 children/year			Annual percent change by year period, %		
	2004-2012	2004-2008	2009-2012	2004-2012	2004-2008	2009-2012
Study cohort	40.2	37.8	43.2	3.2***	6.0***	1.0
(n=10,617)	37.7-42.9	34.7-41.2	42.6-43.7	1.9 - 4.5	3.6-8.5	0.98-1.1
By age group at diabetes diagnosis						
0-6 years (n=2472)	27.8	27.0	28.9	2.2*	6.6***	0.0
	26.3-29.4	24.6-29.6	28.1-29.7	(0.6 - 3.8)	4.5-8.8	-3.3-3.3
7-12 years (n=3690)	44.9	42.2	48.3	3.2***	6.0*	-1.1
	42.0-48.0	38.5-46.3	47.2-49.5	(1.5 - 4.9)	2.3-10.0	-3.3-1.1
13-18 years (n=4455)	47.9	44	52.8	4.1***	5.7***	1.3***
	44.4-51.6	40.6-47.7	51.9-53.7	(3.2 - 5.0)	3.9-7.6	0.9-1.6
By sex						
Girls (n=5087)	39.5	37.1	42.6	3.0***	3.4	1.3
	37.2-41.9	34.8-39.5	41.3-43.9	(1.9 - 4.1)	0.98-7.1	-1.5-4.1
Boys (n=5530)	40.9	38.5	43.9	3.4**	8.5***	-1.1
	37.9-44.1	34.3-43.2	43.1-44.7	(1.5 -5.4)	5.9-11.1	-2.3-1.0
By age group and sex						
0-6 years						
Girls	26.4	25.6	27.4	1.5	2.8	-0.3
	25.1-27.8	23.6-27.9	26.6-28.2	-0.3-3.3	-3.2-9.2	-3.3-2.8
Boys	29.2	28.3	30.3	2.7*	10.0****	0.2
	27.1-31.4	24.7-32.3	29.3-31.3	0.3-5.1	8.0-12.0	-3.4-3.8
7-12 years						
Girls	45.4	43.2	48.1	2.8****	4.6*	2.0
	42.8-48.1	39.9-46.8	46.1-50.2	1.3-4.2	0.3-9.1	-1.9-6.0
Boys	44.5	41.2	48.6	3.6**	7.5*	-4.0****
	40.8-48.5	36.5-46.5	46.1-51.1	1.0-6.2	1.7-13.6	-4.7-(-3.3)
13-18 years						
Girls	46.8	42.2	52.6	4.4****	2.8	2.0
	43.1-50.8	39.9-44.7	50.9-54.3	3.1-5.7	-0.8-6.4	-0.3-4.3
Boys	48.9	45.7	53.0	3.9****	8.4****	0.7
	45.2-52.9	40.7-51.3	52.0-53.9	2.2-5.6	5.7-11.2	-1.0-2.4

Notes: [a] Poisson model estimates with 95% Cis. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05

APPENDIX VI

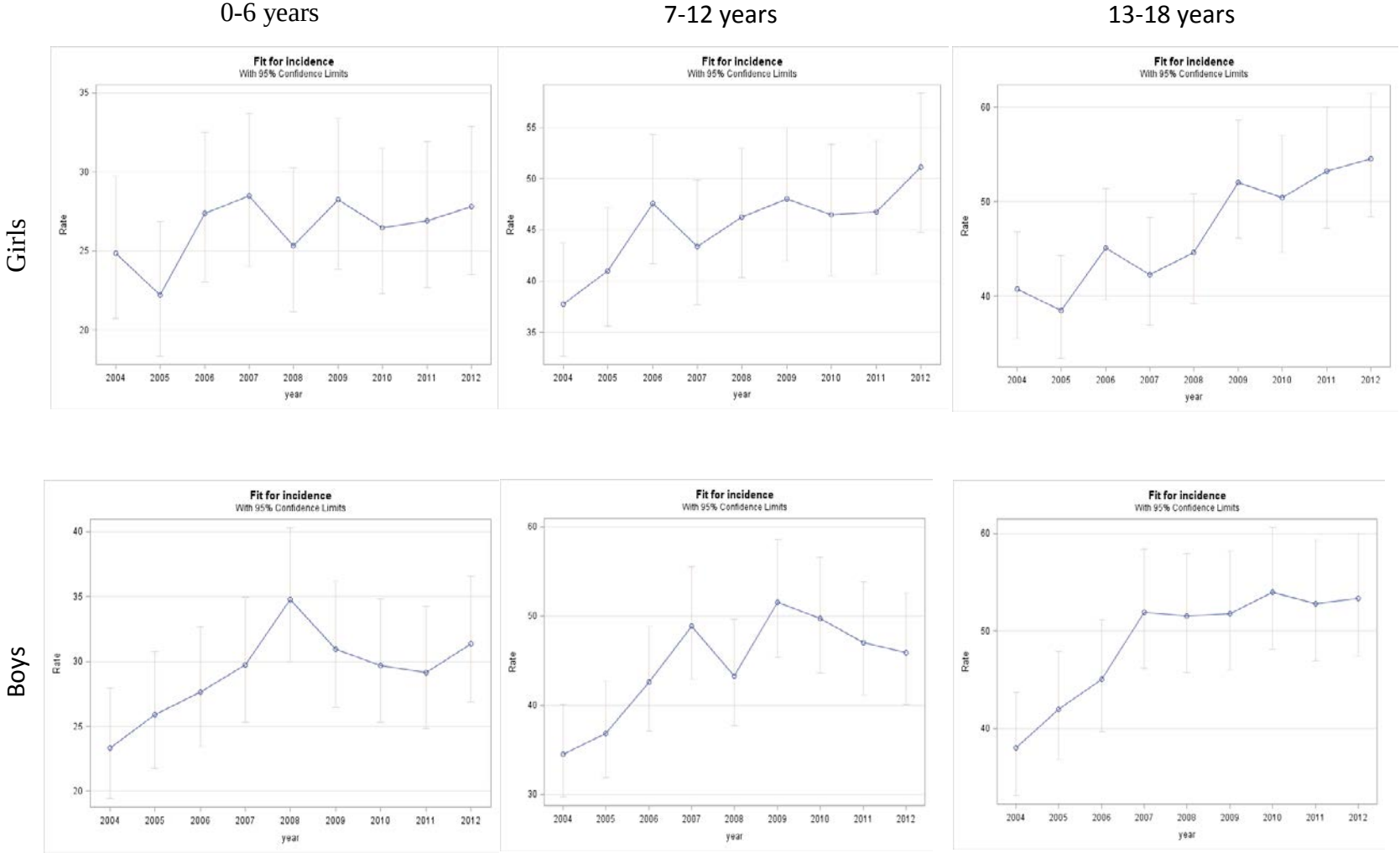
Table: Diabetes incidence rates (IRs) and annual percent change (APC) by Ontario region and year, per 100,000 children/year

Year/year period	Ontario n=10,617		South-Central n=5236		South-Eastern n=1387		South-Western n=3247		Northern Ontario n=747	
		95% CI		95% CI		95% CI		95% CI		95% CI
2004	34.5	32.4-36.8	31.3	29.1-33.7	33.9	31.5-36.4	35.1	32.7-37.8	38.2	35.6-41.1
2005	37.4	35.1-39.8	33.9	31.5-36.4	36.6	34.1-39.3	38.0	35.4-40.8	41.4	38.6-44.3
2006	42.0	39.6-44.5	38.0	35.5-40.7	41.1	38.4-44.0	42.7	39.9-45.7	46.5	43.5-49.6
2007	43.1	40.7-45.7	39.1	36.5-41.8	42.3	39.5-45.2	43.9	41-46.9	47.7	44.7-51.0
2008	43.2	40.8-45.8	39.2	36.6-41.9	42.4	39.6-45.3	44.0	41.1-47	47.8	44.8-51.1
2009	45.1	42.6-47.7	40.8	38.2-43.7	44.2	41.4-47.2	45.8	42.9-48.9	49.9	46.8-53.2
2010	44.3	41.8-46.9	40.1	37.5-42.9	43.4	40.6-46.4	45.0	42.1-48.1	49.0	45.9-52.3
2011	43.0	40.6-45.6	39.0	36.4-41.7	42.2	39.4-45.1	43.8	40.9-46.8	47.6	44.6-50.9
2012	44.5	42.0-47.1	40.3	37.7-43.1	43.6	40.8-46.6	45.2	42.3-48.3	49.2	46.1-52.5
2004-2008	37.8	34.7-41.2	34.9	31.9-38.1	39.8	36.3-43.6	40.6	37.2-44.1	45.4	40.8-50.6
2009-2012	43.2	42.6-43.8	41.9	40.7-43.1	42.7	39.6-46.0	45.2	42.9-47.6	47.5	45.4-49.8
2004-2012	41.9	39.6-44.4	38.0	36.3-39.4	41.1	39.3-42.6	42.6	40.8-44.1	46.4	44.5-48.0
					Estimated APCs by year period[a]					
2004-2008	6.0****	3.6-8.5	6.5****	4.5-8.5	4.9	-0.3-10.4	5.9****	3.2-8.6	6.6*	1.3-12.1
2009-2012	0.0	-1.5-1.6	0.0	-3.1-3.2	-1.3	-9.0 -7.0	1.1	-4.8-6.8	-2.4	-6.1-1.4
2004-2012	2.6****	1.6-3.5	4.1****	2.8-5.5	1.9	1.0-4.1	0.71 2.9***	1.3-4.4	1.6	1.0-3.9

[a] Significance of APC was estimated for each region with a Poisson regression model with IR as an dependent variable and year as an independent variable (for 3 year periods). ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05

APPENDIX VII

Figure: Age-and-sex specific diabetes incidence rates in 2004-2012 (per 100,000 children)



APPENDIX VIII

Table: Generalized linear mixed modelling of a DKA hospital admission probability

	Model 2		Model 3		Model 4		Model 5	
Fixed Effects	F value	Pr>F	F Value	Pr > F	F Value	Pr > F	F Value	Pr > F
Ontario region	3.58	0.01	3.58	0.013	3.52	0.01	1.31	0.27
Year since diabetes diagnosis	0.97	0.33	1.47	0.226	10.1	0.002	6.89	0.008
Socio-demographics								
Age at diagnosis			6.05	0.003	3.8	0.02	5.4	0.004
Sex			3.67	0.05	4.91	0.03	8.12	0.004
Material deprivation			2.71	0.030	3.41	0.009	5.7	0.0001
Rural residence			1.57	0.21	1.37	0.25	0.42	0.62
Main diabetes care provider					4.19	0.0008	5.79	<0.0001
Frequency of physician visits					4.05	0.04	5.18	0.02
Had ED visits for diabetes care					40.08	<.0001	48.32	<.0001
Health status								
Had psychiatrist consultation							23.12	<.0001
Had psychiatrist consultation Rural residence*							4.2	0.02
Comorbidity							40.6	<.0001
*Has comorbidity*Main diabetes care provider*							4.3	0.0006
			Model statistics					
Error variance/intercept	16.1(1.6)***		14.3 (1.6)***		9.6 (1.4)***		6.1 (0.71)***	
Model fit:								
-2 Log Likelihood	13917.65		13674.55		13603.32		13479.28	
AIC & AICC	13929.65		13704.55		13647.32		13541.28	
BIC	13972.06		13810.35		13802.5		13759.94	