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Title	Increasing diabetic ketoacidosis prevalence at diabetes diagnosis among children in Quebec: a population-based retrospective cohort study
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Reviewer 1	Sarah Tsai
Institution	Endocrinology, Children's Hospital of Eastern Ontario, Ottawa, Ont.
General comments (author response in bold)	A few comments: 1. page 3 of 13, introduction, last paragraph, you discuss population burden of DKA - suggest expanding on this with 1 or 2 sentences **In the last paragraph of the introduction, we added a sentence on DKA burden, as follows:** **"DKA is an avoidable complication and the leading cause of death in children less than 15 years of age diagnosed with T1D (Reference: Dahlquist et al. Diabetes care. 2005;28:2384-2387). The population burden of DKA may underscore gaps in health care access and/or in knowledge of the early symptoms of T1D among the lay and medical community."** **The population burden of DKA is also discussed in the second paragraph of the introduction.** **"DKA is an acute avoidable life-threatening complication and the leading cause of preventable hospitalizations, emergency department visits and deaths in the T1D population (1, 6, 7). The economic costs of one DKA hospitalization are high, ranging from $4125 to $11,196 U.S (8). In addition to acute morbidity risk, DKA is also associated with long-term morbidity. Recent studies suggest that DKA at diagnosis predicts poor long-term glycemic control, independent of demographic and socioeconomic factors (9, 10)."** 2. Cohort identification, cannot distinguish T1D vs T2D, suggest adding reference regarding DKA at new onset T2D (you mention this in discussion, but it would be good to have a reference here) **In the Methods section, Cohort identification paragraph, we added:** **"While DKA can occur at diagnosis in both T1D and type 2 diabetes in children, the CCDSS definition does not distinguish between T1D and type 2 diabetes (23)" and added the following reference: Presentation of youth with type 2 diabetes in the Pediatric Diabetes Consortium. Pediatr Diabetes. 2016 Jun;17(4):266-73.** 3. I think that readers would benefit from a little more explanation of exactly what deprivation index involves, maybe 1-2 sentences, readers may not be too familiar with this term **We have further explained what the material and social deprivation indices are in the Methods section, as follows:** **"The material deprivation index is based on employment, education level and income. The social deprivation index is based on the proportion of individuals living alone and the proportion of single-parent families (Reference: Pampalon et al. Canadian journal of public health. 2012;103:S17-22).The material and social deprivation index is a validated index for Canada and was derived by the Institut national de santé publique du Québec based on census dissemination area (Reference: Pampalon et al. Canadian journal**

	of public health. 2012;103:S17-22). To obtain this index, our study cohort was divided across quintiles of their combined material and social deprivation indices (Q1= least deprived, Q5=most deprived)." 4. Please explain why you divided up the age groups into 1-4, 5-11, 12-17. I have no problem with this, but it would be interesting to hear your rationale. Why did you decide to use group instead of age as a more continuous variable? **Please see our response to editor comments (Point 1).** 5. What is involved in determining social deprivation indices, provide reference or more detailed explanation of Q1, Q5 etc. **We have provided the following reference on how the deprivation indices were determined (Pampalon Can J Public Health 2012). We have also provided further details in the Methods section on what these indices are, as follows:** **"The material and social deprivation index is a validated index for Canada. To obtain this index, our study cohort was divided across quintiles of their combined material and social deprivation indices (Q1= least deprived, Q5=most deprived)."** 6. Page 6, 2nd paragraph, Individuals with missing variables were included - please give more details regarding how you addressed the missing variables **The full study cohort was included in the regression models, including those with missing information by adding dummy variables when socioeconomic status or rural status were missing. Importantly, the only variables missing in our study were rural/urban or socioeconomic status, as indicated in the legend of Table 1.** 7. Results - 2nd paragraph, can you provide results on how the rate of DKA changed over time in age groups, was one group increasing more than others? this is not specifically addressed and would add to the paper **Thank you for this input. We found that the trends in DKA rates was the most significant for the > 5-year age group and nonsignificant in the younger age group.** **As compared to the older age groups, children < 5 years of age are at higher risk for DKA due to factors that do not change over time such as faster metabolic decompensation, not being able to verbalize their diabetes symptoms and having more subtle symptoms that are not as apparent as in older children, leading to delayed diagnosis and treatment.** **In the Methods section, Statistical Analysis paragraph, we added:** **"Sub-analyses were performed using multivariate Poisson regression analyses with robust error variance to model the relationship between calendar year and DKA prevalence at disease onset, for each age group (1-4 years, 5-11 years and 12-18 years) and adjusted for sex, rural status and SES."** **In the Results section, 2nd paragraph, the relative changes in DKA rates over time by age- groups were added, as follows:** **"The relative increase in DKA prevalence over the study period was 0.2% per year (RR 1.002; 95% CI, 0.976- 1.029) among children ages 1 to 4 years, 2.7% per year (RR 1.027; 95% CI 1.009-1.046) among those ages 5 to 11 years and**

	2.3% per year (RR 1.023; 95% CI 1.0035-1.043) among children ages 12 to 17 years." **In the Interpretation, we added an explanation for our findings, as follows: "These factors may also explain why we found that DKA risk did not change over time among young children, as these are factors, other than physician awareness, that are not modified by time or interventions."** 8. Interpretation, 3rd paragraph, 1st sentence, grammatical error "reasons...ARE unclear" **This grammatical error was corrected, and the sentence was changed to: "Reasons for our increasing trend are unclear."** 9. Page 8, 2nd paragraph, DKA in younger age groups - all great possible reasons, but need more references **We have added the following references to the paragraph discussing the possible reasons younger age groups are at higher risk of DKA. These references include:** **1) Bui H, To T, Stein R, Fung K, Daneman D. Is diabetic ketoacidosis at disease onset a result of missed diagnosis? The Journal of pediatrics. 2010;156:472-7** **2) Komulainen J, Kulmala P, Savola K, Lounamaa R, Ilonen J, Reijonen H, et al. Clinical, autoimmune, and genetic characteristics of very young children with type 1 diabetes.** **3) Sochett E, Daneman D, Clarson C, Ehrlich R. Factors affecting and patterns of residual insulin secretion during the first year of type 1 (insulin-dependent) diabetes mellitus in children. Diabetologia 1987;30:453-9.** 10. More DKA in smaller communities - could this be provider driven? Perhaps providers who are pediatricians are seeing in larger cities, in smaller cities perhaps individuals with less pediatric training? any evidence for this? **Thank you for this valuable input. We agree that our findings of individuals living in small cities were at higher risk of DKA compared to those in rural areas could possibly be provider driven, specifically related to the distribution of physician supply as we had discussed in our interpretation. In Ontario, low primary care physician supply was associated with higher admissions and emergency visits among children, which we referenced. We theorized in our interpretation that the geographic disparities in DKA rates may be related to the distribution of physician supply; however, this could not be confirmed in our study and requires further exploration. In the Interpretation section, we have modified the sentence as follows:** **"Our observations could be explained, in part, by differing distribution of physician supply and access across regions. This could not be confirmed in our study and requires further exploration."** 11. page 9, please provide reference for insurance being proxy of SES **We have added the following reference for insurance being used as a proxy of SES (Can J Public Health. 2012 Apr 30;103(8 Suppl 2):S17-22.)** 12. Do you think results of your study are generalizable to the rest of Canada? Why or why not?

	We believe that our findings are generalizable to the rest of Canada, as Quebec, like the rest of Canada, has a universal coverage healthcare system in which all outpatient, inpatient, and emergency care is provided by government funding. How health care services are delivered may vary across provinces; however, access to primary care, which is associated with DKA at diabetes diagnosis, is suboptimal across provinces. **We added the following sentence to the Interpretation, study limitation section:** **"Although our study population was restricted to one province, access to primary care, which is associated with DKA at diabetes diagnosis, is suboptimal across all provinces likely giving a generalizable representation of DKA rates at diagnosis across Canada" (Reference: Nakhla et al. CMAJ. 2018;190:E416-e21)** 13. Limitations should be a separate paragraph **This was done.** 14. You've identified an important public health problem, maybe add some details at the end about strategies that have been used to successfully reduce DKA elsewhere (i.e. posters in Italy) **We have added examples of strategies that have been implemented in other countries to reduce DKA rates at diagnosis.** **In the last paragraph of the Interpretation, the following sentences were added:** **"Our results are concerning and underscore the need to increase physician and public awareness of the signs and symptoms of childhood diabetes before DKA develops and to impress upon them the importance of referring children immediately. For instance, an educational prevention program in Parma, Italy, directed at physicians, teachers, and the public alike saw a significant decrease in the prevalence of DKA at diabetes diagnosis." (References: King et al. Pediatric Diabetes. 2012;13:647-51; Vanelli et al. Diabetes Care. 1999;22:7-9)** 15. Reference 4 - capitalization error **Capitalization error was corrected.**
Reviewer 2	Elizabeth Cummings
Institution	Department of Pediatrics, IWK Health Centre, Halifax, NS
General comments (author response in bold)	This paper examines the prevalence of diabetic ketoacidosis at initial presentation of diabetes in children and adolescents based on examination of administrative data from the province of Quebec from 2001 to 2014. The results showed a concerning trend to higher prevalence of DKA at onset of childhood diabetes from 22% to 30% with a relative increase in DKA at presentation of 2% per year. DKA at onset of diabetes was related to younger age and living in a small city but was not associated with material and social deprivation index. 1. Title - Consider adjusting the title to highlight the main finding of an increase in the prevalence of DKA at diabetes onset over time. This may increase the attention to the article for those scanning the journal. **Thank you for this valuable suggestion. We have changed the title as suggested to:**

	"Increasing diabetic ketoacidosis prevalence at diabetes diagnosis among children in Canada: a population-based retrospective cohort study" 2. Abstract - is clear **Thank you.** 3. Background - This is clear and complete. Consider adding a more recent reference from Australia regarding awareness campaigns and DKA prevalence - King B et al. Pediatric Diabetes Vol 13; Issue 8 2012; 647-651. **Thank you. This reference was added in the third paragraph of the introduction.** 4. The research question is clear and focused and is well justified. **Thank you.** 5. Methods - Study design is appropriate and uses administrative data case definitions that are accepted and previously validated/used in the Canadian context. Although the case definition cannot distinguish type 1 from type 2 diabetes, DKA can occur in either type of diabetes and the majority of diabetes in this age-group is type 1, so this is a minor issue. **Thank you.** 6. Results - are interesting, important and well presented. **Thank you.** 7. Interpretation - is appropriate **Thank you.** 8. Figure 1 - The confidence intervals are only shown below the point estimate. It may provide a better picture to show them on both sides of the point estimate. **We apologize for this and thank you for pointing this out. With the original submission the confidence intervals were on both sides of the point estimate; however, upon uploading the figure only the lower CI's were shown. We have corrected Figure 1 and ensured that the confidence intervals are now on both sides of the point estimate with the uploaded version.** Minor Editorial comments 9. Abstract - last sentence - "warrant a need" is redundant - perhaps - "demonstrate a need" **In the abstract, "warrant a need" was changed to "demonstrate a need".** 10. Introduction - first sentence of paragraph 3 - the wording should be "DKA rates … "vary" not varies …and "are" not is inversely…" **Sentence was corrected to read as follows: "DKA rates at T1D diagnosis vary between 12-80% and are inversely correlated with the population incidence of T1D."** 11. Page 10 first sentence - Should be "Reasons for our increasing trend ARE unclear"

	Sentence was corrected to read as follows: "Reasons for our increasing trend are unclear."
Reviewer 3	Elvira Isganaitis
Institution	Division of Integrative Physiology and Metabolism, Pediatrics, Joslin Diabetes Center, Boston, Mass.
General comments (author response in bold)	DKA is one of the most serious acute complications of diabetes, and a report of increasing DKA in a developed population with excellent access to health care would be a cause for concern for physicians and lawmakers alike. The only significant weakness is the uncertainty regarding the accuracy of the diagnosis of DKA based on billing codes. Major comments: 1. P. 6-7, Methods: "Our primary outcome was DKA at the time of a diabetes diagnosis. We identified DKA episodes diagnosed within three days of the date of diagnosis of diabetes and taking place during outpatient or emergency department visits (Physicians Service Claims Database, using the Classification of Diseases' Quebec specific diagnosis codes [ICD-9] 250.1- 250.2) or during a hospitalization (using MED-ECHO hospital data, principal or secondary diagnosis of DKA ICD-9 codes before 2006 and ICD-10 codes E10.10-E14.10 and E10.12-E14.12 after 2006)." How accurate was the diagnosis of DKA based on administrative billing codes? Billing codes have their limitations -- are there any data correlating the billing code to lab values? The U.S. SEARCH study cited by the authors based their case definition of DKA on lab values, in addition to billing diagnosis of DKA. It would helpful to know how many of the participants had ketonemia or ketonuria (without acidosis), versus actual DKA – this may be especially likely in those who were managed in an outpatient setting, or for which no hospitalization was associated with the diagnosis. Would it be possible to access information on how many patients were placed on an insulin drip (in addition to the DKA billing code) as a surrogate for "true" DKA? If there were a significant increase in cases of mild ketonemia (without acidosis), rather than actual DKA diagnoses, this could change the article's implications about delays in diagnosis and treatment of diabetes. Alternatively, the authors could do a sensitivity analysis excluding DKA diagnoses not associated with a hospitalization, which are more likely to be mild ketonemia. A documented rise in rates of DKA diagnosis associated with hospitalization would be especially concerning and would support the key conclusions. **The diagnostic codes we used to identify DKA, ICD-10 CA codes E10.10-E14.10 and E10.12-E14.12, have been used in previous Canadian studies in children to identify DKA within provincial administrative databases (1,2). These codes are also those specified by CIHI to identify DKA hospitalizations (3). We have added these references in our methods section. Unfortunately, with administrative data we do not have access to clinical data, such as laboratory values. However, we did conduct a sensitivity analysis as suggested by the reviewer excluding DKA not associated with hospitalizations which may be mild ketonemia or ketonuria but may also still include DKA episodes. With the exclusion of non-hospitalized DKA codes, we still documented a rise in rates of DKA diagnosis associated with hospitalization, supporting our key conclusions. Please see paragraphs on Sensitivity Analysis in Methods section and Results section.**

	The following sentences were added to the last paragraph of the Results section: **"Among the 1471 children that presented with DKA at diabetes diagnosis, 1402 required a hospitalization. The relative increase in DKA requiring hospitalization over the study period was 1.2% per year (RR 1.012, 95% CI, 1.0002-1.023)."** **1.Shulman R, Stukel TA, Miller FA, Newman A, Daneman D, Wasserman JD, et al. Low socioeconomic status is associated with adverse events in children and teens on insulin pumps under a universal access program: a population-based cohort study. BMJ Open Diabetes Res Care. 2016;4(1): e000239.** **2.Nakhla M, Rahme E, Simard M, Guttmann A. Outcomes associated with a pediatric clinical diabetes network in Ontario: a population-based time-trend analysis. CMAJ Open. 2017;5(3): E586-e93.** **3.Canadian Institute for Health Information. Volume 1—International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) - Tabular List. Ottawa, ON: CIHI; 2012. Available from: https://www.cihi.ca/en/icd_volume_one_2012_en.pdf.** 2. General: No information is presented about race/ethnicity. The manuscript would be strengthened by including this important covariate. **We agree that race/ethnicity is indeed an important clinical variable. Unfortunately, Canadian administrative databases do not contain information on race or ethnicity.** **The following sentence was added to the Interpretation, study limitation section:** **"Further, we could not adjust for other factors associated with DKA such as ethnicity or family history of diabetes, since these are not captured in administrative databases."** Minor comments: 3. P. 5, Methods, line 33: "all encounters with the health care system…" - A small subset of the population might be accessing care through the parallel private health care system – would these be captured within this database? **In Quebec, all hospitalizations, emergency department visits and diabetes care for children with T1D in Quebec are within the public health care system. As such, all patients presenting with DKA in Quebec would be captured in the public health care system. Private insurance companies in Quebec are forbidden to offer services that duplicate those offered by the public system.** **4. P. 8, Results: "We identified 5741 new cases of diabetes."** - would be helpful to provide more detail here – over what time period, for how many person-years of follow-up, etc. Would like to see more information about changes in diabetes incidence according to age. For example, is the increase in DKA prevalence partially attributable to a shift in the age at diabetes diagnosis toward a younger age, as has been documented in several populations. **We clarified the time period where the 5741 individuals with diabetes were**

	identified. In the Results, first paragraph, we added: **"between April 1st, 2001 and March 31st, 2014"** **When examining diabetes incidence according to age, we did not observe a significant increase in diabetes incidence among younger age groups. For example, among individuals ages 1-4 years, the diabetes incidence rate was 25 cases per 100,000 in 2000-2001 compared to 22 cases per 100,000 in 2016-2017. Among individuals aged 5-9 years, the diabetes incidence rate was 25 cases per 100,000 in 2000-2001 compared to 26 cases per 100,000 in 2016-2017. Among individuals ageds10-14 years, the diabetes incidence rate was 27 cases per 100,000 in 2001-2002 compared to 36 cases per 100,000 in 2016-2017. Finally, among individuals ages 15-17 years, the diabetes incidence rate was 35 cases per 100,000 in 2000-2001 compared to 40 cases per 100,000 in 2016-2017.** **When we looked at the relative increase per year, we had adjusted for age. As such, our observed relative increase in DKA prevalence is not attributable to the shift in the age of diabetes diagnosis.** 5. Figure 1. -Would not refer to "T1D incidence", but rather "diabetes incidence" as the authors were not able to distinguish T1D from T2D. **"T1D incidence" was changed to "diabetes incidence" in Figure 1.** 6. Why is only the lower half of the error bars shown – is this in keeping with CMAJ formatting guidelines? Suggest adding the upper half of the error bar. **This error was corrected in Figure 1, which now contains confidence intervals on both sides of the point estimate.** 7. The y-axis on the left does not start at zero, which is a bit misleading. May be clearer if the y-axis on both sides presented the incidence (cases per 1,000 per year), and the age-standardized prevalence (percent) could be presented in another panel. **We adjusted the y-axis of Figure 1 to start at 0.** 8. The Figure legend would benefit from more information, such as the sample size and p-values. **In the legend of Figure 1, we added the sample size and confidence intervals.** 9. Figure would look more polished if a consistent font were used throughout **We adjusted Figure 1 so that a consistent font is used throughout.** 10. Table 1. These data may be conveyed more effectively as a figure rather than in table form. Perhaps the table could be included as a supplement. **Table 1 was included as a supplement.** 11. Introduction: "DKA rates at T1D diagnosis varies between 12-80% and is…" - Grammatical error (rates […] vary […] and are) **This grammatical error was corrected and reads as follows "DKA rates at T1D diagnosis vary between 12-80% and are inversely correlated with the population incidence of T1D"** 12. P. 4, line 42: "jurisdictions"

	- I'm not sure this is quite the right term – perhaps regions or countries? "jurisdictions" was replaced by "regions". 13. P. 4, line 42: missing a period **A period was added.** 14. P. 8, line 22: "Care, NC" - Should be "Cary, NC" **We have corrected this to "Cary, NC".** 15. P. 10, line 15: "… limited and deteriorating access to primary health care in Canada" - Is it possible to use the geographical information (used to derive SES scores) to determine whether DKA risk was higher in areas with especially limited access to care? This would further increase the public health relevance of the authors' findings. **Thank you for this valuable input, unfortunately, we are not able to determine the DKA risks among the different health regions of Quebec, since we do not have the statistical power to perform such an analysis. However, we were able to determine DKA risks based on the rural/urban status of the individual whereby we found that compared to youth living in urban cities, those living in smaller cities had an increased DKA risk at diabetes diagnosis, which requires further investigation.**