PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review
AUTHORS	Fazeli Farsani, Soulmaz; Brodovicz, Kimberly; Soleymanlou, Nima; Marquard, Jan; Wissinger, Erika; Maiese, Brett

VERSION 1 - REVIEW

REVIEWER	Norman Waugh Warwick Medical School, University of Warwick, UK
REVIEW RETURNED	22-Mar-2017

GENERAL COMMENTS	BMJ Open – 2017-016587 Overall, this is a well-conducted review of a somewhat neglected topic, DKA in adults with type 1 diabetes. Most attention has been given to DKA in children. Given that it's a good study, I don't need to say much. It seemed odd to be talking of the "prevalence" of DKA. The authors explain what they mean on page 7, but I think "frequency" would be better than prevalence. My only major concern was that the DKA episodes were not divided into DKA at diagnosis of diabetes and later DKA. The former are less preventable. The authors were limited by what was in the primary studies, some of which did not distinguish between number of DKA episodes and number of patients having DKA. There were many problems with the primary studies and Farsani and colleagues have given a good critique of those. I would have preferred the quality assessment on page 16 to come earlier in the Results section, and the authors might have considered whether some poor quality studies should have been omitted. Another concern is the reliability of the diagnosis of type 1 – were some insulin-treated type 2 diabetics included? The authors address this point on page 9, and paragraph 2 on page 16. Minor points Page 7, end of top paragraph, "sample size of fewer than 50". I would clarify that this refers to patients not episodes of DKA. Page 10, second paragraph. The study from Colorado reported no DKA in patients on MDI. It would be useful to know what proportion of patients were on CSII and MDI. That DKA was seen only amongst those on CSII, might reflect a preponderance of treatment with CSII. On page 14 it is reported that some studies found less DKA on CSII. The Colorado study has one of the poorest quality scores. At foot of page 5, there is a comment about one study using a DKA definition that required admission to hospital. It would be rare for people with DKA not to be admitted. There are occasional deaths before admission.

	Page 22, two-thirds down page, there is a reference to Marian Rewers' study. The DARTS group from Tayside reported that many patients omitted some insulin doses. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes L.A. Donnelly, A.D. Morris, J.M.M. Evans for the DARTS/MEMO collaboration QJM (2007) 100 (6): 345-350.

REVIEWER	Christie Schumacher, PharmD, BCPS, BCACP, BCADM, CDE and Elizabeth Van Dril, PharmD Midwestern University Chicago College of Pharmacy Downers Grove, IL USA
REVIEW RETURNED	31-Mar-2017

GENERAL COMMENTS	Abstract: Page 2: Consider stating why this study was conducted. Was it to evaluate who is at the highest risk? Also , consider stating how this information can be used clinically in the future. Page 2, line 30: Consider changing wording "but with" to "additional studies identified; however, unspecified patient age range.." Page 2, line 19: Consider adding literature to systematic review (SLR) Page 2, line 38: Consider removing "no more than"; or clarify why this terminology was used Page 2, line 42: Consider making more concise (e.g. "women and non-white patients" instead of "woman than men, in non-white than white") Page 2, line 53: Only poorly characterized in epidemiological studies or across primary literature in general? Page 2. Line 53: Consider changing final conclusion sentence to "In an era when the risks versus benefit profile of new antidiabetic therapies are being evaluated, including their potential risk of DKA, there is a clear need to better elucidate the background rate of DKA among adults with T1D." - since most these agents are only approved for use in T2D, would it beneficial to mention the fact that they're being used off label in these patients and phase 3 trials for their use in T1D patients are ongoing, which is why we need to determine the baseline rate and characteristics that place adults with T1D at higher risk for DKA. Strengths and limitations: Second bullet point: Consider "may" instead of "could" and "a wide" instead of "the whole" Introduction: Page 4, line 10: Consider rewording "pancreas are destroyed" Page 4, line 21: Consider changing "newly diagnosed cases each year worldwide" to "new cases diagnosed worldwide each year." Page 4, line 25: Removed % after the number 3. Page 4, line 27: Peak meaning average? Page 4, line 29: Consider removing last sentence in first paragraph as it does not bring relevance to the paper. Page 4, second paragraph: Consider making this paragraph more global as opposed to stating specific percentages for each country. Consider including average ranges and shorten and combine with the first paragraph to make more concise and focused. Page 4, line 49-53: When stating "per 100,000" consider stating "per 100,000 people" or "per 100,000 people with T1D" throughout the entire paper. Page 4, line 58: Replace < with "less than" Page 5: Consider combining the first and third sentence, or bring the

	third sentence after the first sentence for clarity. Also consider defining hyperglycemia, and replace the words “weakness and drowsiness” with “fatigue.” Page 5, line 16: Consider replacing “should be” with “are commonly” and consider adding anion gap to as a marker of acidosis. Page 5, line 34: You have specific data for Scotland and the US. Do you have more global data? I would consider removing country specific data (thoughtout the entire introduction) and creating global generalizations that are region focused. You have data for specific countries in your introduction that do not align with the countries of the literature reviewed in the SLR, so it may be beneficial to categorize by region or ethnicity. Page 5, line 38: 54-76% of all diabetes-related deaths are due to DKA? Does this not include DM-related CV causes of deaths? This sentence is confusing as it states, “among all diabetes-related deaths, 54-76% can be attributed to DKA”; however, you stated previously that the mortality rate for DKA was very low. Page 5, line 38-40: Consider replacing “Risk factors for DKA (or higher frequency of experiencing DKA)” with “Risk factors associated with a higher frequency of DKA” Page 5, line 42: Your sentence regarding patients being of younger age at the time of DKA hospitalization is slightly confusing. Consider refocusing this paragraph to consider all risk factors, such as younger age, duration of T1D, insulin use, CSII vs. injections, etc. Page 5, line 49: “The prevalence of DKA at presentation” of what? Consider replacing “presentation” with “diagnosis”, if that’s what this is referring to. Page 5, line 49: Consider starting new paragraph and talking about the difference in T1D in pediatrics vs. adults. In adults with a later onset of diagnosis, they may retain beta-cell function and have a lower risk of DKA compared to pediatrics. They also may not become insulin-dependent as quickly, which may lower rate as well. All this should be introduced in the introduction, since some is discussed in the discussion. Page 5, line 49: Having a prevalence range from 12-81%, is listed in only reference 32. Reference 33 includes 29 studies in 12 different Arab countries captured 4,688 type 1 diabetes patients with overall rates of 46.7% patients presented with DKA, ranging from a low of 17% in Egypt to a high of 100% in Morocco, Algeria and Tunisia and this data is not mentioned in the sentence. Also, the percentages vary significantly based on country. This should be addressed as well, since a range from 12 – 81% is confusing for readers to extrapolate. You could consider removing all numbers and stating “the prevelance of DKA at diagnosis in pediatrics is well documented; however, information on the prevalence or incidence in adults with DKA at T1D diagnosis is limited.” This would remove confusion with large ranges and you could continue to use both reference 32 and 33. Page 5, line 51: Consider adding “in adults with T1D” to be more specific Page 6, line 10: The abstract mentions “population-based and other observational studies” but other observational studies was not mentioned in the objective. Does this need to be included for consistency? Page 6, line 10: How was duplication from SLRs and MA’s that covered the same observational studies as those that were individually included eliminated? Methods: Page 7, line 14 – 19: Consider stating that age at diagnosis, duration of therapy, insulin use, and other confounding variables can all effect

	the risk and confound results. What steps were taken to minimize this? Page 7, line 19 – 29: Consider explaining why you excluded RCTs and and other types of studies for the audience. Page 7, line 49: Consider coma after “outcomes” and before “if” Page 8, line 4-6: Unsure if authors need to reference the results of the search here? Consider saving for the results section. Page 8, line 12: Consider clarifying response rate Page 8, line 30: Consider referencing the results of the analysis here? Consider placing in results section? Results: Page 8, line 49: Insert space between “1” and “summarizes” Page 9, line 3: Recommend listing out which ones were specifically in Israel or China - instead of “or” Page 9, top paragraph: Consider describing the incidence and prevalence by geographic region? For example, grouping the results by saying: “Overall, eight studies reported incidence rate with a range of 0-263 per 1,000 PYs (insert references); the lowest rate reported in Isreal36 and North America45 and the highest reported in China44 (Figure 2). Eleven studies reported prevalence with a range 0-128 per 1,000 people (insert references); the lowest prevalence was reported in Sweden43 and the highest in Canada23 (Figure 3a).” Page 9, line 34: Capitalize “registry” for consistency Page 9, line 32 – 34: Consider stating how DKA was evaluated in all cases. You account for 11 of 19 through self-reported questionairres and hospitalization records. When reviewing appendix 2, nine of the cases were ascertained through the medical record, 2 though hospitalizations, 4 through a self-reported patient questionnaire, and 1 was not reported. Consider listing all ascertainment sources. Page 9, line 34 - 42: Does it matter that logistics regression models were similar between participant-reported vs. clinic-documented DKA when participant-reported event rates were still higher? Major limitation? Page 9, line 51 – 53: In those studies that were not 1:1 female:male, which gender was more often represented? Page 10, line 1: Consider changing “most” to “the majority” Page 10, line 4: 50-60% of patients with T1D treated with CSII; representative of clinical practice and overall T1D population? Only 11 of 19 studies reported on insulin delivery methods. Curious to see if any of these individual studies were looking at CSII’s ability to decrease DKA rates in this patient population; hence the high rate of CSII use Page 10, line 16 and 18: Include “studies” after values in parentheses Page 10, line 23 – 26: You state 20 cases were identified at baseline and 0 events at 12-year follow-up. This exemplifies that risk decreases over time since diagnosis and should be highlighted throughout your intro and discussion as well as a confounding varable in limitations, that time since diagnosis was not reported. Page 10, line 27: Consider replacing “at Year 18 of follow-up” with “at the 18-year follow-up in another cohort” to stay consistent with the first part of the sentence. Page 10, line 29: Consider adding “s” to MDI since “injections” is plural and this is how it was defined above in methods Page 12, line 8: Consider changing “a numerical (but not statistically significant) reduction” to “a nonsignificant, but numerical reduction” Page 12, line 36-47: Consider breaking up run-on sentence. Insert period after “other countries” on line 40 and consider starting sentence with “Investigators attribute this discrepancy…”

	Page 12, line 47 – 49: Consider changing “It also seems likely (although not explicitly described in the publication)” to “although not explicitly described in the publication, it seems likely” Page 12, line 53: Consider changing “a third” to “one third” Page 13, line 25-29: Can you really say elderly are associated with the lowest prevalence of DKA when a good portion of this prevalence rate overlaps? (e.g. 40-60 cases per 1000) ◊ per 1000 what?; consider using lower and higher versus lowest and highest Page 13, line 34-38: If recall time affects proper self-reporting of DKA events, what limitations have to be drawn about the other studies and the accuracy of their prevalence of DKA by age group? Page 14, line 3-5: Were presence of depression and poor/fair versus excellent glycemic control listed and defined in Appendix 1 as variables to examine in the analysis? Page 14, line 14-16: Remove parentheses and state “over a 12-month period Page 14, line 38: Again using lower prevalence rather than lowest Page 14, line 44: Replace injectable insulin with MDIs Page 15, line 14 – 18: Should insulin use or medications utilized be added to the list of confounding factors. Page 15, line 42: add “s” to MDIs (multiple injections) Pate 17, line 25-29: Do patients over-report episodes of DKA, are they aware of the definition? Should self-reported DKA be used for analysis in those individual studies over clinic-determined DKA? Discussion: Page 18, first paragraph of discussion: Consider describing discussion results as recommended in previous review of results section. Page 18, line 25: Consider “Of the” instead of “Out of” Page 18, line 36 – 40: Consider adjusting countries to country-specific studies; so instead of North America, changing to North American studies Page 19, line 27: Consider changing “did not describe whether (or how) the included patient cohort differed” to “did not describe whether and the degree to which the patient cohort differed” Page 20, line 29: Consider changing “Many (24)” to “Twenty-four” Page 20, line 33: Consider replacing “combined diabetic population (T1D and T2D combined).” to “combined population of patients with T1D and T2D.” Page 21, line 21 – 23: Was this expansion of included studies included in the methods section above? Consider including. Page 21, line 31 – Page 22, line 10: Is this a summary of studies that were identified in the literature search but ultimately excluded from the review? If so, clarify that the last two studies discussed (citation 48 and 49)were excluded from the analysis and why. If

	these studies were not excluded from the analysis, consider removing them from the paragraph or discussing them elsewhere. Page 22, line 27: Consider changing “vs” to “compared to” Page 22, line 51: Consider removing parentheses around “at all ages”. Page 22, line 55: Consider changing “vs” to “versus” Page 22, line 57: Consider changing “vs” to “compared to” Page 23, line 8: Consider defining level of uncontrolled HbA1c, as was done with the adult studies Page 23, line 12-25: The reporting of prevalence of DKA at presentation for children with T1D and T2D (citation 53) does not contribute much to the discussion of the SLR, recommend removing. Page 23, line 34 – 36: Age at diagnosis of T1D, duration of T1D, and medication (insulin) use should be included as well. Pae 24, line 8: Consider stating other reasons why your audience needs to know this information and expand on why it is important clinically. Conclusion: Page 24, line 36: Consider ending sentence after “T1D patients.’ Begin following sentence with “From the currently available” Page 24, line 40: Consider replacing “it is clear that there remains an unmet need to address the prevention of this serious complication of T1D among adult patients.” with “it is apparent that there remains a need to identify those at highest risk for this serious complication in an effort to prevent its occurrence among adults with T1D.” Also, the authors did not mention prevention of DKA thoughout the paper; however it is incorporated in the conclusion. Consider integrating it throughout the paper.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Norman Waugh
Institution and Country: Warwick Medical School, University of Warwick, UK Competing Interests: None.
Overall, this is a well-conducted review of a somewhat neglected topic, DKA in adults with type 1 diabetes. Most attention has been given to DKA in children. Given that it’s a good study, I don’t need to say much.
It seemed odd to be talking of the “prevalence” of DKA. The authors explain what they mean on page 7, but I think “frequency” would be better than prevalence.

Response: We appreciate the reviewer’s feedback, however, since “prevalence” and not “frequency” was the term used during the literature search and study selection we prefer to keep “prevalence”.

My only major concern was that the DKA episodes were not divided into DKA at diagnosis of diabetes and later DKA. The former are less preventable.
The authors were limited by what was in the primary studies, some of which did not distinguish between number of DKA episodes and number of patients having DKA. There were many problems with the primary studies and Farsani and colleagues have given a good critique of those. I would have preferred the quality assessment on page 16 to come earlier in the Results section, and the authors might have considered whether some poor quality studies should have been omitted.
Another concern is the reliability of the diagnosis of type 1 – were some insulin-treated type 2 diabetics included? The authors address this point on page 9, and paragraph 2 on page 16.

Response: Thank you for raising this important point about the timing of DKA episodes in relation to

T1D diagnosis. The following text has been added to the Methods section (page 7) to clarify the assessment of DKA episodes for this review: “DKA outcomes were considered only for patients who were previously identified as having T1D; publications reporting data only for DKA episodes at presentation or diagnosis of T1D were excluded.”
The main objective of our study was to report what is known about the frequency of DKA in adults with T1D; therefore we started the results section with this information followed by the quality assessment. We prefer to keep this order but if it is very crucial for the reviewer we would be willing to change this order and present the quality assessment section earlier.

Minor points
Page 7, end of top paragraph, “sample size of fewer than 50”. I would clarify that this refers to patients not episodes of DKA.

Response: The text has been revised to make clear that this restriction refers to number of patients.

Page 10, second paragraph. The study from Colorado reported no DKA in patients on MDI. It would be useful to know what proportion of patients were on CSII and MDI. That DKA was seen only amongst those on CSII, might reflect a preponderance of treatment with CSII. On page 14 it is reported that some studies found less DKA on CSII. The Colorado study has one of the poorest quality scores.
Response: The reviewer raises a valid point about the interpretation of these data. In the Colorado study, most patients (58%) were treated with MDI. The relative proportion of patients using each treatment method has been added to the manuscript text for clarity. We agree that this study was of overall poor quality, but it was 1 of only 2 studies conducted in North America that reported incidence rate data for DKA, which is why these data were included.
At foot of page 5, there is a comment about one study using a DKA definition that required admission to hospital. It would be rare for people with DKA not to be admitted. There are occasional deaths before admission.

Response: We thank the reviewer for this clarification, and have removed the sentence on the DKA definition requiring hospitalization.

Page 22, two-thirds down page, there is a reference to Marian Rewers’ study. The DARTS group from Tayside reported that many patients omitted some insulin doses. Adherence to insulin and its association with glycaemic control in patients with type 2 diabetes L.A. Donnelly, A.D. Morris, J.M.M. Evans for the DARTS/MEMO collaboration QJM (2007) 100 (6): 345-350.

Response: We have updated the discussion section and referred to the study about the “Adherence to insulin treatment, glycemic control, and ketoacidosis in insulin-dependent diabetes mellitus” by the DARTS group.

Reviewer: 2
Reviewer Name: Christie Schumacher, PharmD, BCPS, BCACP, BCADM, CDE and Elizabeth Van Dril, PharmD Institution and Country: Midwestern University Chicago College of Pharmacy Downers Grove, IL, USA Competing Interests: None

Response: We thank the reviewers for their very detailed comments and suggestions throughout the manuscript; please note that the abstract has been substantially revised and restructured according to an editorial request. Additionally, we have incorporated the reviewers’ recommendations as needed to improve the clarity and readability of the manuscript. Detailed changes are addressed below.

Abstract:
Page 2: Consider stating why this study was conducted. Was it to evaluate who is at the highest risk? Also , consider stating how this information can be used clinically in the future.
Page 2, line 30: Consider changing wording “but with” to “additional studies identified; however, unspecified patient age range..”
Page 2, line 19: Consider adding literature to systematic review (SLR)
Page 2, line 38: Consider removing “no more than”; or clarify why this terminology was used
Page 2, line 42: Consider making more concise (e.g. “women and non-white patients” instead of “woman than men, in non-white than white”)
Page 2, line 53: Only poorly characterized in epidemiological studies or across primary literature in general?
Page 2. Line 53: Consider changing final conclusion sentence to “In an era when the risks versus benefit profile of new antidiabetic therapies are being evaluated, including their potential risk of DKA, there is a clear need to better elucidate the background rate of DKA among adults with T1D.” - since most these agents are only approved for use in T2D, would it beneficial to mention the fact that they’re being used off label in these patients and phase 3 trials for their use in T1D patients are ongoing, which is why we need to determine the baseline rate and characteristics that place adults with T1D at higher risk for DKA.
Strengths and limitations: Second bullet point: Consider “may” instead of “could” and “a wide” instead of “the whole”

Response: As mentioned above, the abstract has been substantially revised and restructured according to an editorial request. All changes have been made, but we cannot consider reviewers suggestion about addition of off-label use because there is not enough information available on the off-label use of oral antidiabetic medications in adults with T1D.

Introduction:
Page 4, line 10: Consider rewording “pancreas are destroyed”
Page 4, line 21: Consider changing “newly diagnosed cases each year worldwide” to “new cases diagnosed worldwide each year.”
Page 4, line 25: Removed % after the number 3.
Page 4, line 27: Peak meaning average?
Page 4, line 29: Consider removing last sentence in first paragraph as it does not bring relevance to the paper.
Page 4, line 49-53: When stating “per 100,000” consider stating “per 100,000 people” or “per 100,000 people with T1D” throughout the entire paper.
Page 4, line 58: Replace < with “less than”
Page 5, line 38-40: Consider replacing “Risk factors for DKA (or higher frequency of experiencing DKA)” with “Risk factors associated with a higher frequency of DKA”
Page 5, line 42: Your sentence regarding patients being of younger age at the time of DKA hospitalization is slightly confusing. Consider refocusing this paragraph to consider all risk factors, such as younger age, duration of T1D, insulin use, CSII vs. injections, etc.
Page 5, line 49: “The prevalence of DKA at presentation” of what? Consider replacing “presentation” with “diagnosis”, if that’s what this is referring to.
Page 5, line 51: Consider adding “in adults with T1D” to be more specific Page 6, line 10: The abstract mentions “population-based and other observational studies” but other observational studies were not mentioned in the objective. Does this need to be included for consistency?

Response: We thank the reviewers for the very careful review of the Introduction and have incorporated several of the suggested changes to improve the precision of the wording throughout this section of the manuscript.

Page 4, second paragraph: Consider making this paragraph more global as opposed to stating specific percentages for each country. Consider including average ranges and shorten and combine with the first paragraph to make more concise and focused.

Response: Diagnosis of T1D typically occurs in childhood; therefore limited information is available on the rates of T1D in adults. That is why we decided to present the rates in both children and adults. In the second paragraph rates of T1D from individual countries that were part of our systematic review were presented. We did not incorporate this suggestion but if it is important for the reviewer we would be willing to reconsider.

Page 5: Consider combining the first and third sentence, or bring the third sentence after the first sentence for clarity. Also consider defining hyperglycemia, and replace the words “weakness and drowsiness” with “fatigue.”

Response: All changes made but “weakness and drowsiness” were not replaced with “fatigue” as we would prefer to use the language from the reference we cited.

Page 5, line 16: Consider replacing “should be” with “are commonly” and consider adding anion gap to as a marker of acidosis.

Response: “should be” replaced with “are commonly” but anion gap not added as a marker of acidosis as this was not a marker we came across in our literature searching.

Page 5, line 34: You have specific data for Scotland and the US. Do you have more global data? I would consider removing country specific data (thoughtout the entire introduction) and creating global generalizations that are region focused. You have data for specific countries in your introduction that do not align with the countries of the literature reviewed in the SLR, so it may be beneficial to categorize by region or ethnicity.

Response: We thank the reviewers for these comments and follow-up questions. We had hoped to highlight a few examples of the wide variability in DKA-related mortality reported in a few recent studies rather than provide an in-depth overview of the topic, as mortality is not a focus of this review.

Page 5, line 38: 54-76% of all diabetes-related deaths are due to DKA? Does this not include DM-related CV causes of deaths? This sentence is confusing as it states, “among all diabetes-related deaths, 54-76% can be attributed to DKA”; however, you stated previously that the mortality rate for DKA was very low.

Response: We thank the reviewers for the question and have attempted to provide some additional clarification by editing the manuscript wording. The text has been revised to clarify that this refers to T1D-related deaths among young adults. Due to the high proportion of children/adolescents and young adults with excess mortality resulting from T1D, the impact of CV-related deaths (which are generally more frequent among older adults and the elderly than children/adolescents) is less significant than is seen in T2D patients. While the overall mortality rate for DKA is very low, among those patients who die from diabetes-related complications, acute metabolic events such as DKA contribute to a substantial proportion (54-76%) of deaths.

Page 5, line 49: Consider starting new paragraph and talking about the difference in T1D in pediatrics vs. adults. In adults with a later onset of diagnosis, they may retain beta-cell function and have a lower risk of DKA compared to pediatrics. They also may not become insulin-dependent as quickly, which may lower rate as well. All this should be introduced in the introduction, since some is discussed in the discussion.

Response: We thank the reviewers for raising this interesting point; however, it was not the intent of this SLR to attempt to explain the underlying physiologic mechanisms that may contribute to differences in DKA rates between children and adults, as this topic, while certainly relevant, is beyond the scope of the current review. We included some discussion of pediatric T1D patients to provide some context from the available published literature (as literature on adult T1D patients is much more limited).

Page 5, line 49: Having a prevalence range from 12-81%, is listed in only reference 32. Reference 33 includes 29 studies in 12 different Arab countries captured 4,688 type 1 diabetes patients with overall rates of 46.7% patients presented with DKA, ranging from a low of 17% in Egypt to a high of 100% in Morocco, Algeria and Tunisia and this data is not mentioned in the sentence. Also, the percentages vary significantly based on country. This should be addressed as well, since a range from 12 – 81% is confusing for readers to extrapolate. You could consider removing all numbers and stating "the prevelance of DKA at diagnosis in pediatrics is well documented; however, information on the prevalence or incidence in adults with DKA at T1D diagnosis is limited." This would remove confusion with large ranges and you could continue to use both reference 32 and 33.

Response: We thank the reviewers for the thoughtful assessment of how better to present these data and have incorporated the suggested revisions.

Page 6, line 10: How was duplication from SLRs and MA's that covered the same observational studies as those that were individually included eliminated?

Response: We thank the reviewers for the question on the SLR methodology. No relevant SLR/MAs were identified by this review so this step was not needed.

Methods:
Page 7, line 14 – 19: Consider stating that age at diagnosis, duration of therapy, insulin use, and other confounding variables can all effect the risk and confound results. What steps were taken to minimize this?
Response: We thank the reviewers for the additional question on the SLR methodology. This study is a narrative description of the results of the SLR; individual studies included in the SLR may or may not have accounted for potential confounding factors in the reported results. Many of the included studies described logistic regression analyses adjusted for several of the parameters the reviewers list above. However, as we describe in the manuscript, in many instances DKA was not a primary outcome of interest in the included studies, and therefore the evaluation of potential confounding factors was not reported. In addition, no quantitative meta-analyses were explored or conducted as a part of this study; therefore an evaluation of potential confounding factors across the included studies was not performed.
Page 7, line 19 – 29: Consider explaining why you excluded RCTs and and other types of studies for the audience.

Response: We thank the reviewers for the comment and have added text to the methods section clarifying that interventional studies were excluded from the review because the outcomes of interest were estimates of incidence and prevalence from non-interventional studies.

Page 7, line 49: Consider coma after "outcomes" and before "if"
Page 8, line 4-6: Unsure if authors need to reference the results of the search here? Consider saving for the results section.
Page 8, line 12: Consider clarifying response rate Page 8, line 30: Consider referencing the results of the analysis here? Consider placing in results section?

Response: This additional information and explanatory text was included in the Methods section so that other investigators could replicate and/or update the results of this review in subsequent studies, as reproducibility is a central tenet of such types of reviews.

Results:
Page 8, line 49: Insert space between “1” and “summarizes”
Page 9, line 3: Recommend listing out which ones were specifically in Israel or China - instead of “or”
Page 10, line 27: Consider replacing “at Year 18 of follow-up” with “at the 18-year follow-up in another cohort” to stay consistent with the first part of the sentence.
Page 10, line 29: Consider adding “s” to MDI since “injections” is plural and this is how it was defined above in methods Page 12, line 8: Consider changing “a numerical (but not statistically significant) reduction” to “a nonsignificant, but numerical reduction”
Page 12, line 36-47: Consider breaking up run-on sentence. Insert period after “other countries” on line 40 and consider starting sentence with “Investigators attribute this discrepancy…”
Page 12, line 47 – 49: Consider changing “It also seems likely (although not explicitly described in the publication)” to “although not explicitly described in the publication, it seems likely”
Page 13, line 25-29: Can you really say elderly are associated with the lowest prevalence of DKA when a good portion of this prevalence rate overlaps? (e.g. 40-60 cases per 1000) à per 1000 what?; consider using lower and higher versus lowest and highest.
Page 14, line 14-16: Remove parentheses and state “over a 12-month period
Page 15, line 42: add “s” to MDIs (multiple injections)
Page 10, line 1: Consider changing “most” to “the majority”
Page 12, line 53: Consider changing “a third” to “one third”
Page 14, line 38: Again using lower prevalence rather than lowest
Page 19, line 27: Consider changing “did not describe whether (or how) the included patient cohort differed” to “did not describe whether and the degree to which the patient cohort differed”
Page 20, line 29: Consider changing “Many (24)” to “Twenty-four”

Response: We have incorporated above recommendations throughout the Results section to improve the clarity, consistency, and readability of the results.

Page 9, top paragraph: Consider describing the incidence and prevalence by geographic region? For example, grouping the results by saying: “Overall, eight studies reported incidence rate with a range of 0-263 per 1,000 PYs (insert references); the lowest rate reported in Isreal36 and North America45 and the highest reported in China44 (Figure 2). Eleven studies reported prevalence with a range 0-128 per 1,000 people (insert references); the lowest prevalence was reported in Sweden43 and the highest in Canada23 (Figure 3a).”

Response: Thank you for this suggestion, however, we believe the results, as described 2 paragraphs beyond this one, do summarize incidence rate and prevalence by region (starting with the section entitled, “Overall incidence and prevalence of DKA in North America”.

Page 9, line 34: Capitalize “registry” for consistency Page 9, line 32 – 34: Consider stating how DKA was evaluated in all cases. You account for 11 of 19 through self-reported questionairres and hospitalization records. When reviewing appendix 2, nine of the cases were ascertained through the medical record, 2 though hospitalizations, 4 through a self-reported patient questionnaire, and 1 was not reported. Consider listing all ascertainment sources.

Response: we cannot consider these suggestions because we think that addition of this information to the text will make the paragraph more difficult to read, and would be redundant with the information presented in Appendix 2.

Page 9, line 34 - 42: Does it matter that logistics regression models were similar between participant-reported vs. clinic-documented DKA when participant-reported event rates were still higher? Major limitation?

Response: The manuscript text has been revised for clarity. These studies evaluated potential associations between patient characteristics and DKA events; the analyses were run with both sets of data for DKA (patient-reported and clinic-documented) with similar results. We do not view this as a limitation.

Page 9, line 51 – 53: In those studies that were not 1:1 female:male, which gender was more often represented?

Response: In the 3 studies in which the female:male ratio was not approximately 1:1, women generally represented a greater proportion of the population than men.

Page 10, line 4: 50-60% of patients with T1D treated with CSII; representative of clinical practice and overall T1D population? Only 11 of 19 studies reported on insulin delivery methods. Curious to see if any of these individual studies were looking at CSII's ability to decrease DKA rates in this patient population; hence the high rate of CSII use Page 10, line 16 and 18: Include "studies" after values in parentheses Page 10, line 23 – 26: You state 20 cases were identified at baseline and 0 events at 12-year follow-up. This exemplifies that risk decreases over time since diagnosis and should be highlighted throughout your intro and discussion as well as a confounding varable in limitations, that time since diagnosis was not reported.

Response: It would be of interest to carefully compare the patient populations described in the studies included in the SLR with the broader patient population treated in clinical practice, but such an analysis is beyond the scope of the current study. We have included an evaluation of the representativeness of the cohorts in the included studies as part of the quality assessment for the SLR, as well as a description of the potential limitations of patient registry-based studies.
We reported the potential risk factors for DKA as identified by the authors of the included studies, several of which did evaluate data for time since diagnosis and include this parameter as a potential confounding factor in their analyses, as described in the manuscript. Since de novo analyses of factors impacting the rate of DKA were not conducted as part of this SLR, a discussion of potential confounding variables on the rate of DKA also was not included.

Page 13, line 34-38: If recall time affects proper self-reporting of DKA events, what limitations have to be drawn about the other studies and the accuracy of their prevalence of DKA by age group?

Response: We raised this point in reference to recall time affecting the actual number of events that occur (i.e., greater likelihood of a DKA episode when a longer time period is assessed). We did not intend to infer other limitations regarding accuracy of DKA events based on this point.

Page 14, line 3-5: Were presence of depression and poor/fair versus excellent glycemic control listed and defined in Appendix 1 as variables to examine in the analysis?

Response: As the SLR was intended to be a qualitative narrative synthesis of the available evidence (rather than a quantitative analysis), specific definitions and lists of potential risk factors were not determined a priori in the SLR protocol. Rather, the protocol states that data on potential risk factors will be captured as reported in the included studies (without specifying individual risk factors), so that all available relevant data could be captured. We have updated the SLR protocol to reflect this.

Page 14, line 44: Replace injectable insulin with MDIs

Response: This change was not made, as not all injectable insulins are given as MDIs.

Page 15, line 14 – 18: Should insulin use or medications utilized be added to the list of confounding factors.

Response: These factors were not included in the list of potential confounding factors as they were not identified in any of the studies reviewed.

Pate 17, line 25-29: Do patients over-report episodes of DKA, are they aware of the definition? Should self-reported DKA be used for analysis in those individual studies over clinic-determined DKA?

Response: We reported the conclusions of the authors of the primary studies regarding the discrepancies between patient self-reported episodes of DKA and medical records-confirmed episodes of DKA. In most instances in these studies, patient self-reported data were used in the primary analyses, and frequently analyses were conducted with both sets of data.

Discussion:
Page 18, first paragraph of discussion: Consider describing discussion results as recommended in previous review of results section.
Page 18, line 25: Consider “Of the” instead of “Out of”
Page 18, line 36 – 40: Consider adjusting countries to country-specific studies; so instead of North America, changing to North American studies
Page 20, line 33: Consider replacing “combined diabetic population (T1D and T2D combined).” to “combined population of patients with T1D and T2D.”
Page 22, line 27: Consider changing “vs” to “compared to”
Page 22, line 51: Consider removing parentheses around “at all ages”.
Page 22, line 55: Consider changing “vs” to “versus”
Page 22, line 57: Consider changing “vs” to “compared to”
Page 23, line 34 – 36: Age at diagnosis of T1D, duration of T1D, and medication (insulin) use should be included as well.

Response: We have incorporated the above recommendations.

Page 21, line 21 – 23: Was this expansion of included studies included in the methods section above? Consider including.

Response: We thank the reviewers for raising this valid point and have added the relevant text describing the expansion of included studies to the Methods section.

Page 21, line 31 – Page 22, line 10: Is this a summary of studies that were identified in the literature search but ultimately excluded from the review? If so, clarify that the last two studies discussed (citation 48 and 49) were excluded from the analysis and why. If these studies were not excluded from the analysis, consider removing them from the paragraph or discussing them elsewhere.

Response: Citations 48 and 49 were excluded from the review due to a lack of patient demographic information, as described in the manuscript.

Page 23, line 8: Consider defining level of uncontrolled HbA1c, as was done with the adult studies
Page 23, line 12-25: The reporting of prevalence of DKA at presentation for children with T1D and T2D (citation 53) does not contribute much to the discussion of the SLR, recommend removing.

Response: The suggested text has been deleted to make the Discussion section more concise. Uncontrolled diabetes was not explicitly defined in the Rewers study; regression analyses found significant associations between DKA events and increasing HbA1c levels.

Page 24, line 8: Consider stating other reasons why your audience needs to know this information and expand on why it is important clinically.

Response: We have explained in the discussion section that because DKA is a recently recognized potential adverse event associated with some approved treatments for T2D, such as sodium-glucose cotransporter-2 inhibitors, and phase 3 trials are being conducted to determine the risk/benefit profile of the use of these therapies in T1D patients, it would be prudent to better elucidate the expected background rate of DKA among adults with T1D.

Conclusion:
Page 24, line 36: Consider ending sentence after “T1D patients.’ Begin following sentence with “From the currently available”

Response: Change made.

Page 24, line 40: Consider replacing “it is clear that there remains an unmet need to address the prevention of this serious complication of T1D among adult patients.” with “it is apparent that there remains a need to identify those at highest risk for this serious complication in an effort to prevent its occurrence among adults with T1D.” Also, the authors did not mention prevention of DKA thoughout the paper; however it is incorporated in the conclusion. Consider integrating it throughout the paper.

Response: We prefer to keep the original wording.

VERSION 2 – REVIEW

REVIEWER	Christie Schumacher Midwestern University Chicago College of Pharmacy 555 31st Street Downer Grove, IL 60515, USA
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	Abstract: Page 2: Consider stating why this study was conducted. Was it to evaluate who is at the highest risk? Also , consider stating how this information can be used clinically in the future. Page 2, line 10: Consider “geographical region” instead of “location” to be more specific. Page 2, line 29: Consider changing “and a second reviewer screened additionally approximately 20% of the publications” to “and a second reviewer performed an additional screening of approximately 20% of the publications” Page 2, line 44: Consider splitting into separate sentences, ending the first sentence at “1,000 PYs”, and starting next sentence with “Eleven studies report prevalence with a range of 0-128 per 1,000

	people." Page 2, line 49: Consider separating and rewording final sentence of the results section into two separate more concise thoughts; for example, "Subgroup analyses were performed using data from no more than two studies per subgroup. There was a higher prevalence of DKA reported in women, non-whites and patients treated with insulin injections compared to men, whites and patients using continuous subcutaneous insulin infusion pumps, respectively." Introduction: Page 4, line 10: Consider rewording "pancreas are destroyed." Page 4, line 14: Consider rewording "in order to survive" to "for survival." Page 4, line 25: Remove % after the number 3. Page 4, line 27: Consider clarifying the meaning of "peak"; is this a mean, median, mode? Page 4, line 29: Consider removing last sentence in first paragraph since "life expectancy" is not directly relevant to the incidence and prevalence of DKA in T1D adults. Page 4, line 49-53: Consider noting the lowest and highest incidence rates (and their corresponding geographic location), to limit overwhelming the audience with statistics; for example "Incidence of T1D varies by age and geographical location; ranging from 4.9 per 100,000 people in Austria to 61.7 per 100,000 people in the US.8-11" Page 4, line 49-53: When stating "per 100,000" consider stating "per 100,000 people." Page 5: Consider combining the first and third sentence, or bring the third sentence after the first sentence for clarity. Also consider replacing the words "weakness and drowsiness" with "fatigue." Page 5, line 12: Consider adding anion gap as a marker of acidosis. Page 5, line 21: Consider clarifying what type of "pump failure"; define continuous subcutaneous insulin infusion (CSII) pump here before using in line 45 below. Methods: Page 6, line 36-40: Consider clarifying how citations of studies in non-English languages were considered (and subsequently excluded since line 36 states only those that were published in English were included). Page 7, line 30: Consider rewording "there were so few population-based studies found" to "there was limited population-based studies in the peer-reviewed literature." Page 7, line 34: Consider removing "outcomes" from the term "epidemiology outcomes" Page 7, line 53: Consider substituting "Clinical outcomes of interest" with "Data of interest" since incidence rates and prevalence

	themselves are not clinical outcomes Results Page 9, line 23: Consider rewording “and three publications in Israel or China” to “two publications in Israel and one publication in China” for clarity Page 9, line 53: Consider alternate phrase for “based on data” since it is used later in the sentence; for example “using data” or “reporting data” Page 10, line 3: Consider changing "based on" to "as identified by" to eliminate repetitive use of the phrase Page 10, line 42-49: Stating “observational cohorts found that the incidence of DKA showed a general reduction over time,” suggests incidence of DKA decreased with increasing age. Would it be more appropriate to just note the minimum and maximum incidence rates for the North American rate and include these statistics (line 42 through 49) in the results based on age section? Page 10, line 49-55: Again, discussing incidence with regards to differences in type of insulin administration (MDI vs. CSII) may be better emphasized in the section discussing results by subgroup. Page 11, line 27: Consider adding “respectively” after “103 per 1,000 people and 128 per 1,000 people” and clarify which prevalence corresponds to which database(s); could consider combining rates with previous sentence that discusses databases utilized Page 12, line 18: Consider changing “DKA results” to “DKA incidence” to be more specific Page 12, line 32-34: Consider noting just the prevalence rates from this study here; report trends on age in later sections Page 12, line 34: Consider replacing "this period" with the defined duration of the longitudinal study Page 14, line 27-29: Consider replacing “vs” with “versus” in all instances Page 14, line 49-51: Was presence of depression or psychiatric symptoms identified as a predefined subgroup for analysis? Page 15, line 3: Consider discussing HbA1c cutoff for poor versus fair versus good glycemic control in the introduction; was this identified as a predefined subgroup for analysis? Discussion Page 22, line 49 through page 23, line 51: Consider removing the discussion of trends of DKA in pediatrics. Is this section relevant to the objectives of this SLR? Conclusions Page 24, line 58: Consider adding "female gender and non-white ethnicity" as factors for increased risk of DKA, as well?

	Page 25, line 10: Consider adding “adult patients with T1D” after “per 1000”. Remove "of T1D among adult patients.”

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Christie Schumacher
Institution and Country: Midwestern University Chicago College of Pharmacy, USA Competing Interests: None declared

Abstract:
Page 2: Consider stating why this study was conducted. Was it to evaluate who is at the highest risk? Also, consider stating how this information can be used clinically in the future.
Response: Following the editor’s recommendation we checked abstracts of other systematic reviews that have been recently published in BMJ Open for what information/ sub-headings to include; there was no “background” section in the abstract so a description of why the study was conducted is outside the scope of the recommended abstract structure. Furthermore word limit of the abstract (300 words) does not allow a detailed description regarding how this information could be used clinically in the future, however, we do describe the need for this information because DKA in adults with T1D has been poorly characterized, and there is a need to better elucidate the risk-benefit profiles of new antidiabetic therapies, including the potential risk of DKA.
Page 2, line 10: Consider “geographical region” instead of “location” to be more specific.
Response: Done.
Page 2, line 29: Consider changing “and a second reviewer screened additionally approximately 20% of the publications” to “and a second reviewer performed an additional screening of approximately 20% of the publications”
Response: Done.
Page 2, line 44: Consider splitting into separate sentences, ending the first sentence at “1,000 PYs”, and starting next sentence with “Eleven studies report prevalence with a range of 0-128 per 1,000 people.”
Response: Done.
Page 2, line 49: Consider separating and rewording final sentence of the results section into two separate more concise thoughts; for example, “Subgroup analyses were performed using data from no more than two studies per subgroup. There was a higher prevalence of DKA reported in women, non-whites and patients treated with insulin injections compared to men, whites and patients using continuous subcutaneous insulin infusion pumps, respectively.”
Response: Done.
Introduction:
Page 4, line 10: Consider rewording “pancreas are destroyed.”
Response: Done.
Page 4, line 14: Consider rewording “in order to survive” to “for survival.”
Response: Done.
Page 4, line 25: Remove % after the number 3.
Response: Done.
Page 4, line 27: Consider clarifying the meaning of “peak”; is this a mean, median, mode?
Response: Done.
Page 4, line 29: Consider removing last sentence in first paragraph since “life expectancy” is not directly relevant to the incidence and prevalence of DKA in T1D adults.
Response: Done.
Page 4, line 49-53: Consider noting the lowest and highest incidence rates (and their corresponding geographic location), to limit overwhelming the audience with statistics; for example “Incidence of T1D

varies by age and geographical location; ranging from 4.9 per 100,000 people in Austria to 61.7 per 100,000 people in the US.8-11”
Response: Done.
Page 4, line 49-53: When stating “per 100,000” consider stating “per 100,000 people.”
Response: Done.
Page 5: Consider combining the first and third sentence, or bring the third sentence after the first sentence for clarity. Also consider replacing the words “weakness and drowsiness” with “fatigue.”
Response: Done.
Page 5, line 12: Consider adding anion gap as a marker of acidosis.
Response: The text was modified accordingly.
Page 5, line 21: Consider clarifying what type of “pump failure”; define continuous subcutaneous insulin infusion (CSII) pump here before using in line 45 below.
Response: Done.
Methods:
Page 6, line 36-40: Consider clarifying how citations of studies in non-English languages were considered (and subsequently excluded since line 36 states only those that were published in English were included).
Response: Additional information regarding how non-English language citations were considered and subsequently excluded has been included in the Methods; please note that a more in depth description of the exclusion of these studies based on a review of the English language abstracts was already included in the Discussion section.
Page 7, line 30: Consider rewording “there were so few population-based studies found” to “there was limited population-based studies in the peer-reviewed literature.”
Response: Done.
Page 7, line 34: Consider removing “outcomes” from the term “epidemiology outcomes”
Response: Done.
Page 7, line 53: Consider substituting “Clinical outcomes of interest” with “Data of interest” since incidence rates and prevalence themselves are not clinical outcomes
Response: Done.
Results:
Page 9, line 23: Consider rewording “and three publications in Israel or China” to “two publications in Israel and one publication in China” for clarity
Response: Done.
Page 9, line 53: Consider alternate phrase for “based on data” since it is used later in the sentence; for example “using data” or “reporting data”
Response: Done.
Page 10, line 3: Consider changing "based on" to "as identified by" to eliminate repetitive use of the phrase
Response: Done.
Page 10, line 42-49: Stating “observational cohorts found that the incidence of DKA showed a general reduction over time,” suggests incidence of DKA decreased with increasing age. Would it be more appropriate to just note the minimum and maximum incidence rates for the North American rate and include these statistics (line 42 through 49) in the results based on age section?
Response: This description refers to a temporal trend in a given study (incidence of DKA reduced over time). We have reworded slightly in order to make this temporal trend clearer. We prefer not to include this information in the age section, as that section focuses on comparisons of DKA in different ages/age groups within a given study.
Page 10, line 49-55: Again, discussing incidence with regards to differences in type of insulin administration (MDI vs. CSII) may be better emphasized in the section discussing results by subgroup.
Response: Your comment is noted and we agree it could be relevant to discuss the difference in DKA with regards to insulin administration in a section dedicated to subgroup results; however, the current

subgroup section consists of studies that described DKA prevalence only (not incidence). The study you are referring to includes DKA incidence rate, and so we felt it best fit it in the description of DKA incidence (which had no further subgroup data to discuss) and was not relevant to include with the DKA prevalence-specific subgroup data.
Page 11, line 27: Consider adding “respectively” after “103 per 1,000 people and 128 per 1,000 people” and clarify which prevalence corresponds to which database(s); could consider combining rates with previous sentence that discusses databases utilized
Response: This section describes 2 analyses from Canada that used all 4 databases; the data from each database were linked by the study authors, and the resulting prevalence estimates were calculated. Clarifying information was added to the manuscript
Page 12, line 18: Consider changing “DKA results” to “DKA incidence” to be more specific
Response: Done.
Page 12, line 32-34: Consider noting just the prevalence rates from this study here; report trends on age in later sections
Response: The authors calculate a separate prevalence for each age in this study (ages 18, 19, 20, 21, 22, 23, and 24) not 1 overall DKA prevalence; thus, the reason for the description by age. It was not possible for us to reliably hand-calculate an overall DKA prevalence due to different proportions of missing data in each age. We have added a note in the result section that the authors calculated the prevalence by each 1 year of age and also mentioned the study in the prevalence trend by age sub-section further below (p. 13).
Page 12, line 34: Consider replacing "this period" with the defined duration of the longitudinal study
Response: Done; additional details on the study’s duration and time period added to the manuscript.
Page 14, line 27-29: Consider replacing “vs” with “versus” in all instances
Response: Change from “vs” to “versus” made throughout manuscript.
Page 14, line 49-51: Was presence of depression or psychiatric symptoms identified as a predefined subgroup for analysis?
Response: No.
Page 15, line 3: Consider discussing HbA1c cutoff for poor versus fair versus good glycemic control in the introduction; was this identified as a predefined subgroup for analysis?
Response: The sub-section on risk factors for DKA was included as a potential point of interest to some readers; as already noted, this was not the main focus of the SLR, which was to determine the incidence rate and prevalence of DKA (ie, to be included in the SLR, a study had to have data on incidence rate or prevalence, or the ability for us to calculate it; it did not have to have data on risk factors). We believe the inclusion of individual descriptions of each risk factor, including HbA1c cut-off for poor vs fair control, is outside of the scope of the manuscript.
Discussion:
Page 22, line 49 through page 23, line 51: Consider removing the discussion of trends of DKA in pediatrics. Is this section relevant to the objectives of this SLR?
Response: We cannot consider this suggestion because we believe that the readers of the journal may benefit from this information in the discussion.
Conclusions:
Page 24, line 58: Consider adding "female gender and non-white ethnicity" as factors for increased risk of DKA, as well?
Response: Female sex was added to the list, but non-white ethnicity was not, as the (limited) results on this characteristic are conflicting.
Page 25, line 10: Consider adding “adult patients with T1D” after “per 1000”. Remove "of T1D among adult patients.”
Response: Done.