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Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review

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ABSTRACT

OBJECTIVES

To summarize the available data on the incidence and prevalence of diabetic ketoacidosis (DKA) in adult patients with type 1 diabetes mellitus (T1D), and to evaluate trends in the incidence and prevalence of DKA for the overall patient population and specific subgroups by age, sex, geographic location, ethnicity, and type of insulin administration.

DESIGN

A systematic review was performed (SLR) in PubMed and Embase (between January 1, 2000 and June 23, 2016). Outcomes of interest were incidence rate and prevalence of DKA reported in peer-reviewed population-based and other observational studies.

RESULTS

Out of 1,082 articles reviewed, 19 publications met the inclusion and exclusion criteria, with two additional studies identified but with unspecified patient age range and therefore not included in the SLR. Overall, eight studies reported incidence with a range of 0–56 per 1,000 person-years (PYs), with one outlying study reporting an incidence rate of 263 per 1,000 PYs and 11 studies reporting prevalence with a range of 0–128 per 1,000 people. Prevalence of DKA decreased with increasing age. Based on data from no more than two studies, there was a higher prevalence of DKA reported in women than men, in non-white than white ethnic groups, and in patients treated with insulin injections than those using continuous subcutaneous insulin infusion pumps.

CONCLUSIONS

To our knowledge, this is the first SLR on the epidemiology of DKA in adults with T1D. Despite an increasing prevalence of T1D in recent years, DKA in adults has been poorly characterized in epidemiological studies. In an era when the benefit-risk of new antidiabetic therapies is being assessed, including potential risk of DKA, there is a clear need for further investigation to better elucidate the expected background rate of DKA among adults with T1D.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- To our knowledge, this is the first literature review to systematically assess and summarize the incidence rate and prevalence of DKA in adults with T1D.
- Both young adults and the elderly were included in this SLR, so the results could be applicable across the whole spectrum of adult T1D patients.
- The quality of included studies was assessed using a standardized tool (the JBI prevalence studies quality assessment tool).
- This review, like any SLR, is subject to publication bias, as an SLR inherently relies upon data available in the published literature.
- Studies not published in English were excluded from the SLR, as were studies of fewer than 50 patients.

KEY WORDS: diabetic ketoacidosis; type 1 diabetes mellitus; systematic literature review; incidence; prevalence; epidemiology;

Introduction

Diabetes is a disease characterized by high blood glucose resulting from abnormal insulin production, function, or both.[1] Type 1 diabetes mellitus (T1D) develops when insulin-producing beta cells in the pancreas are destroyed.[1] This destruction is modulated by the body's immune system and leads to a limitation in, or complete cessation of, the production and secretion of insulin, which results in the need for external insulin delivery in order to survive.[1] T1D typically follows an acute clinical course, with patients presenting with polyuria, polydipsia, and weight loss.[2] According to the International Diabetes Federation (IDF), approximately 542,000 children 0−14 years of age have T1D, with 86,000 newly diagnosed cases each year worldwide.[3] While there are geographical differences, the overall annual increase in the incidence of T1D is estimated at approximately 3%−4%.[3, 4] Diagnosis of T1D typically occurs in childhood; in the United States (US), the peak age at diagnosis is approximately 14 years. Compared to adults without the disease, patients with T1D at age 20 years have an estimated loss of life expectancy of approximately 13 years for women and 11 years for men.[5, 6]

Information regarding the epidemiology of T1D specifically in adults is scarce; many epidemiological studies of adult patients categorize those with blood glucose levels above a certain threshold as simply diabetic, without providing more detailed data on the relative proportions of patients with T1D versus type 2 diabetes mellitus (T2D).[3] Approximately 5% of adult-diagnosed cases of diabetes are diagnosed as T1D,[1] although an Italian study has shown rates of T1D as high as 50% of incident cases of diabetes among normal-weight adults (aged 30−54 years).[7] Incidence of T1D varies by age and is reported to be 9.0−61.7 per 100,000 in the US, 4.9−6.7 per 100,000 in Austria, 9.4−55.0 per 100,000 in Sweden, 12.2 per 100,000 in the UK, 15.9 per 100,000 in Finland, and 22−38.2 per 100,000 in Sardinia.[8-11] A recent systematic literature review (SLR) reported the incidence of T1D to be 1.5 times higher in males than in females <40 years of age.[8]

Diabetic ketoacidosis (DKA) is a major acute metabolic complication of T1D that is typically marked by acidosis, ketosis, and usually hyperglycemia.[12-14] The symptoms of uncontrolled diabetes that may lead to development of DKA are typically of short duration and include polyuria, polydipsia, polyphagia, weight loss, vomiting, abdominal pain, weakness, and drowsiness.[12, 14] Diabetic ketoacidosis is diagnosed in different ways, but typically the following three factors should be present: elevated plasma glucose (>250 mg/dL), ketones in serum or urine, and acidosis (serum bicarbonate <18 mEg/L and/or pH <7.30).[12] Management of DKA includes fluid and electrolyte therapy, insulin therapy, treatment of any identified triggering causes (eg, pump failure, sepsis, pneumonia, acute pancreatitis, cerebrovascular accident, myocardial infarction, stroke, trauma, medications that affect carbohydrate metabolism), and monitoring of therapy and resultant complications.[12, 14, 15] Excessively rapid fluid resuscitation should be avoided to prevent cerebral edema, a rare but debilitating and potentially fatal complication of DKA.[12] While inpatient mortality rates for DKA are generally very low (<1% in Scotland [16] and in the US [17]), rates vary substantially based on healthcare setting; a recent analysis conducted in India reported that up to 30% of hospitalized DKA cases result in inpatient death.[15] Among all diabetes-related deaths, 54%–76% can be attributed to DKA.[18-21] Risk factors for DKA (or higher frequency of experiencing DKA) may include younger age at time of DKA hospitalization,[22, 23] higher mean glycosylated hemoglobin A1c (HbA1c),[13, 22-25] infection,[26] continuous subcutaneous insulin infusion (CSII) pump failure,[27, 28] lower socioeconomic status/household income,[13, 22, 24] lower physical activity level,[29] and psychiatric symptoms/depression.[22, 30, 31] The prevalence of DKA at presentation ranges from 12%–81% in pediatric patients with T1D [32, 33]; information on the prevalence or incidence in adults is limited. One study using the T1D Exchange Clinic Registry in the US found that 4.8% of participants reported one or more DKA events (requiring self-reported overnight hospitalization) in the previous 12 months.[13] Since in this study the DKA case definition required hospitalization, this

may represent an underestimate of the true number of DKA cases, some of which may not have resulted in hospitalization. The objectives of this SLR were to summarize the available epidemiological data (incidence rate and prevalence) for DKA in adult patients (aged ≥18 years) with T1D from population-based studies and to evaluate trends in the evidence for the overall patient population and specific subgroups (age, sex, geography, ethnicity, and type of insulin administration such as CSII or multiple daily injections [MDIs]).

Methods

Search strategy and selection process

This systematic review was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[34] The Study protocol (including search strategy and search terms) was developed and accepted by all authors prior to commencement of the search and can be found in Appendix 1. MEDLINE (via PubMed) and Embase databases were searched for articles published between January 1, 2000 and June 23, 2016 (date of search execution). The searches were filtered for human studies, but no language restrictions or geographic limitations were applied to the search strategy. Note that only studies published in English were included. Relevant studies published in other languages were noted during screening and a list of these citations reviewed for consideration. Included studies were peer-reviewed, and ongoing studies without peer-reviewed publication (eg conference abstracts) were excluded. The search results were combined in a referencing software database, and duplicate records were removed.

Upon second-pass review, the following criteria were applied. The targeted population was males and females aged at least 18 years with T1D. When sufficient data were available in the publications to permit determination of the patients' age range (for example, mean age and standard deviation [SD] or standard error), the relevant calculations were performed to

determine eligibility for inclusion (for example, mean age ± three SD as an estimate of the range of study patients' age). If the mean age was reported and the calculated age for minus three SDs was <18 years, the study was excluded, unless the study population was explicitly described as adults aged ≥18 years. Studies of mixed populations (pediatric and adult patients and/or T1D and T2D) were included only if stratified data were reported for adult T1D patients. This review was not restricted by specific interventions or comparators and included all T1D patients, regardless of treatment. Type of insulin and method of administration were of interest and were captured when these data were available. Peer-reviewed population-based observational studies, SLRs, and meta-analyses of human studies were included. Excluded study designs were randomized controlled trials/clinical trials, interventional studies, preclinical or animal studies, editorials, letters, commentaries, case studies, reports or case series, theses and dissertations, narrative literature reviews, small studies (sample size of fewer than 50), guidelines, and unpublished studies (eg, conference abstracts).

Data extraction and analysis

Data extraction was conducted using a Microsoft® Excel file with standardized definitions for each data element that was extracted from each study (see Appendix 1). Clinical outcomes of interest were incidence rate of DKA (number of new DKA events out of accumulated patient time under study, in person-years [PYs]) and prevalence of DKA (number of DKA events among the total number of patients at risk). Data on risk factors and clinical parameters associated with DKA events were also extracted when reported in the included publications. When sufficient data were available in the published literature to allow computation of these outcomes if not specifically reported by the authors (for example, the number or proportion of patients who experienced a DKA event over a defined time period), the appropriate calculations were performed and are noted as such. For two publications, cumulative incidence was calculated (number of new DKA events out of total patients at risk) because data on incidence rates were

not directly reported in the publications. Results from data extraction, including incidence rate, prevalence, and risk factors for DKA, can be found in Appendices 2 and 3.

The quality of included studies was assessed by a trained epidemiologist, with consideration of the study design, disease ascertainment, response rate (if applicable), definition of DKA, representativeness of the study population, and major potential biases. A table describing these factors for each included study can be found in this report (Table 1). Additionally, a standardized quality assessment tool, the Joanna Briggs Institute (JBI) Critical Appraisal Tools "Checklist for Prevalence Studies" (available at http://joannabriggs.org/research/critical-appraisal-tools.html), was selected as an appropriate tool for assessment of the included study designs. Quality assessment of each included study using the JBI Checklist for Prevalence Studies was undertaken independently by two reviewers, with any discrepancies resolved by a third reviewer. The results of the quality assessment using the JBI tool can be found in Appendix 4.

Patient involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. No patients were asked to advise on interpretation or reporting of results. There are no plans to disseminate the results of the research to patient communities.

Results

Figure 1summarizes the literature review process, including the number of records identified, the screening and eligibility results, and the final list of included references. Out of 1,082 articles identified through the initial search, 19 peer-reviewed observational study publications met the inclusion and exclusion criteria; no SLRs or meta-analyses were identified that met the inclusion and exclusion criteria. There were 11 publications in North America (US and Canada),[13, 22-24, 31,

[35-40] five publications in Europe,[29, 30, 41-43] and three publications in Israel or China.[25, 44, 45] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[25, 29, 30, 36, 37, 41, 44, 45] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[13, 22-24, 31, 35, 38-40, 42, 43] The lowest incidence rates were reported in Israel and North America (both 0 events per 1,000 PYs)[36, 45] and the highest in China (263 events per 1,000 PYs)[44] (Figure 2). The lowest prevalence was reported in Sweden (0 per 1,000 people)[43] and the highest in Canada (127.9 per 1,000 people)[23] (Figure 3a).

In terms of baseline characteristics, patient selection, and descriptions of outcomes, there were some broad similarities across studies included in this review. In most studies, specific definitions or diagnostic criteria for T1D were not described, and some studies did not fully report patient baseline demographic information such as patient ethnicity or insulin delivery method. Standardized measurements of DKA events were not frequently utilized, as many studies (seven of 19) relied on patient self-report of DKA episodes or hospitalization records (four of 19). Three publications[13, 24, 31] based on data from the T1D Exchange Clinic registry directly compared DKA data based on patient self-reported and clinic-documented events and found that, while the frequency of participant-reported DKA events was higher than clinic-reported events based on medical records, results from logistic regression models were similar for both sets of data.[13] Few exclusion criteria were applied to the patient populations, most commonly pregnancy and lack of available data. The age range of patient cohorts varied across studies, with some investigations (two of 19) restricted to young adults only (approximately 18–26 years of age), four studies focused on adults aged approximately 20–55 years, and most (12 studies) evaluating adults of all ages, including those aged over 65 years. Most (16 of 19) studies had approximately a 1:1 male-to-female ratio of patients. Ethnicity of the patient cohorts was only reported in eight studies; when reported, the vast majority of patients (>80%) were of white non-Hispanic ethnicity. In the publications providing data on insulin delivery method in

unselected populations (11 of 19 studies), most (50%–60%) patients were treated with CSII. While the number of studies providing data on insulin delivery method was limited, there seemed to be an overall trend toward an increasing proportion of CSII users in more recent publications/study periods compared with older investigations.

Overall incidence and prevalence of DKA in North America

Eleven studies conducted in North America (US and Canada) reported incidence rate (2) or prevalence (9) for DKA events in adults with T1D (Appendix 2). Results from two long-term observational cohorts found that the incidence of DKA showed a general reduction over time, with an incidence rate of approximately 20 cases per 1,000 PYs at baseline to 0 events at the 12-year follow-up in one cohort and a decrease from approximately 30 cases per 1,000 PYs at baseline to <10 cases per 1,000 PYs at Year 18 of follow-up.[36] A US-based study from a single clinic in Colorado compared CSII pump users to patients treated with MDI [37]; over the study period of approximately 1 year, only patients treated with CSII experienced any DKA events. In this investigation, the cumulative incidence of DKA was calculated to be 55.6 per 1,000 people for CSII users.

All of the publications describing prevalence of DKA in the US were based on data from the T1D Exchange Clinic Registry, although each investigation evaluated a slightly different patient population. All of these studies relied on patient self-report to determine occurrence of DKA events, and the recall period varied from three to 12 months. For most studies of the larger patient population from the registry, prevalence ranged from approximately 50 to 100 per 1,000 people.[13, 24, 35, 40] Slightly higher DKA prevalence than that reported in the US-based studies was observed in two analyses of Canadian data using the following databases: Diabetes, Hypertension, and Cholesterol Center in Calgary, Alberta Inpatient Discharge Abstract Database, Alberta Kidney Disease Network, and Statistics Canada 2006 Census Data.[22, 23] In

these linked database studies, calculated prevalence was found to be 103 per 1,000 people [23] and 128 per 1,000 people.[22] These Canadian studies relied on linked data from hospital inpatient admissions rather than patient self-report.

Overall incidence and prevalence of DKA in Europe

In very broad terms, the incidence rates and prevalence reported for European studies (Appendix 2) were similar to those described in investigations conducted in North America; however, these trends should be considered with substantial caution given the very small number of European publications reporting each outcome. Only five publications described the epidemiology of DKA in adult patient populations in Europe; two reported on patients from the Diabetes-Patienten-Verlaufsdokumentation (DPV) database, which includes patients in Germany and Austria [29, 42]; and three evaluated small single-center patient cohorts.[30, 41, 43] In all cases, DKA events were ascertained based on patient medical records.

Incidence rates ranged from approximately 8 cases per 1,000 PYs (calculated rate based on hospital admissions for DKA) in a study of 113 young adults in Oxfordshire, England [30] to 51.3 cases per 1,000 PYs (reported rate based on pH <7.3 or hospital admission for DKA) for over 18,000 adult patients selected from the DPV database.[29] A Slovenian single-center study of patients treated with CSII [41] provided sufficient data to calculate cumulative incidence of 27.2 cases per 1,000, a lower value than that observed in a similar US-based study (55.6 per 1,000).[37] It should be noted that while the study period was unclear in the US investigation, based on publication date (2004 for the US study), it is likely that the Slovenian study (with a study period through 2011) included more recent data. This may have had an impact on DKA results given the technological improvements in insulin pumps and glucose monitoring over this period; indeed, the US study reported that the majority of DKA events recorded were due to pump malfunctions.

Prevalence of DKA was reported in two European studies.[42, 43] One single-center longitudinal study of 104 patients performed in Sweden [43] found a numerical (but not statistically significant) reduction in DKA cases with increasing year of age from 18 to 24 years (prevalence ranged from 0 to 60 cases per 1,000 people over this period). A cross-sectional analysis of patients from the DPV database examining the association of variability in basal insulin rates with various outcomes reported the prevalence of DKA as 39 cases per 1,000 people,[42] also a slightly lower value than the prevalence data reported for US- or Canadian-based studies.

Overall incidence of DKA in other regions

Three studies conducted in other regions reported only incidence rate data (Appendix 2), with very low rates observed in two studies based on patient medical records from the same tertiary care facility in Israel [25, 45] and very high rates described in a multicenter study conducted in tertiary care units in a single province in China.[44] The low incidence rates in the Israeli studies (ranging from 0 to 40 cases per 1,000 PY) may reflect some selection bias in the patient population treated at this single center.[25, 45] In the Chinese study,[44] the authors acknowledge that the incidence rate observed in their study (263 per 1,000 PY) is considerably higher than values cited in published reports from other countries and attribute this discrepancy, at least in part, to differences in national healthcare systems, which may limit access to routine healthcare for some T1D patients in China, as well as infrequent self-monitoring of blood glucose by patients and inappropriate treatment or errors in diabetes management. It also seems likely (although not explicitly described in the publication) that this study reported the incidence rate of all DKA events during the study period, rather than only the first instance of DKA for each patient. The authors stated that in this study, more than a third (34.4%) of DKA events represented recurrent (two or more) episodes of DKA for 3.8% of patients, suggesting that a small population of very high-risk patients contributed substantially to the overall incidence rate.

DKA prevalence by age

Five publications from the US-based T1D Exchange Clinic Registry [13, 24, 35, 38, 40] reported prevalence of DKA among adults with T1D with outcome data stratified by age (Figure 3b). Four of the studies examined a broad sample of adult patients aged 18 to >90 years; one analysis [24] focused solely on young adults. Given the design of the registry, all five studies relied on patient self-report of past DKA events; three publications [13, 24, 35] examined the prior 12-month period and two [38, 40] queried patients about the previous three months. There was a general trend of decreasing DKA prevalence with increasing age observed across most studies providing age-stratified data. Young adults (aged 18 years to 25 years) had the highest prevalence of DKA (100−120 cases per 1,000 in studies with 12-month recall and 40−80 cases per 1,000 in studies with three-month recall), while the elderly (aged ≥65 years) had the lowest prevalence of DKA (38−60 cases per 1,000 in studies with 12-month recall). The only exception to this trend was a study in which prevalence of DKA was similar across all three adult age ranges (18−25 years, 26−49 years, and ≥50 years).[38] The DKA data in this particular investigation may have been affected by the study requirement that all patients had an annual follow-up visit at which HbA1c was measured and the shorter duration of recall for DKA events (three months). There was no information on incidence rate stratified by patient age reported in any studies identified by this SLR.

DKA prevalence by other patient subgroups of interest

Subgroup data for patients categorized according to clinical or demographic characteristics other than age, such as sex, ethnicity, insulin delivery method, glycemic control, and depression comorbidity were very limited, with data available from only 1 or 2 studies. As with patient stratification by age, only data on DKA prevalence were available for the other categorical variables reviewed. Based on these limited data, higher prevalence of DKA was observed for

women vs men, non-white vs white ethnicities, depressed vs non-depressed patients, patients with fair/poor vs excellent glycemic control, and patients treated with insulin injections compared to those using CSII (Figure 3b).[13, 31, 38, 39]

In a single study designed to investigate cross-sectional associations between patient characteristics and DKA events,[13] female patients had a higher prevalence of DKA (over the previous 12-month period) than male patients (55 vs 40 cases per 1,000 people, respectively). This study also reported a prevalence of DKA in white non-Hispanic patients of 43 per 1,000, while all other ethnicities had considerably higher prevalence of DKA, ranging from 81 per 1,000 (other race/ethnicity) to 121 per 1,000 (black non-Hispanic) during the same study period.[13] Higher prevalence of DKA was observed among depressed patients (110 per 1,000 for patients with at least one DKA event in the previous three months) than non-depressed patients (40 per 1,000 for patients with at least one DKA event in the previous three months).[31]

DKA was more prevalent in patients with fair or poor glycemic control, defined as HbA1c ≥8.5% (120 per 1,000 for patients with at least one DKA event in the previous 12 months).[39] In contrast, the lowest prevalence of DKA was reported for patients with excellent glycemic control, defined as HbA1c <6.5% (10 per 1,000 for patients with at least one DKA event in the prior 12 months).[39] Patients treated with CSII had lower prevalence of DKA than did patients using injectable insulin.[13, 38] This trend was seen across multiple age groups in one study.[38] However, duration of treatment with a CSII may affect prevalence of DKA, as data for patients who had recently (within the prior year) initiated pump therapy had similar rates of DKA to participants treated with insulin injections (both groups had 54 events per 1,000), and the lower DKA prevalence (43 events per 1,000) was observed only in patients who had been treated with a CSII for at least the previous year.[13] It should be noted that these numerical trends did not demonstrate a statistically significant difference between insulin delivery groups in this study.

DKA risk factors and associations

Over half of the included studies (13 publications) reported at least some data on risk factors or patient characteristics associated with DKA events [13, 22-25, 29-31, 38, 40, 42, 44, 45] (Appendix 3). Almost all of these investigations utilized multiple regression analyses to evaluate the associations between baseline parameters and risk of DKA, adjusted for potential confounding factors such as age, sex, body mass index (BMI), and duration of diabetes.[13, 22-25, 29-31, 38, 42, 44] Two of the studies that investigated risk factors associated with DKA only provided qualitative summaries of the associations.[38, 45]

Several studies identified patient characteristics that were significantly associated with increased risk of DKA.[13, 22, 24, 25, 38, 44] The most frequently reported parameters correlating with DKA events were higher HbA1c/poor glycemic control,[13, 22, 24, 25, 38, 44] lower socioeconomic status (based on income, formal education, and private insurance or some combination thereof),[13, 22, 24, 44] depression/psychiatric symptoms or diagnosis at baseline,[22, 30, 31] and female sex.[13, 24, 44] Regarding the patient subgroups of interest, some conflicting data were presented for the relationship between DKA events and ethnicity or insulin delivery method. In a population restricted to young adults only (aged 18 years to 25 years) from the T1D Exchange Clinic Registry, Cengiz and colleagues [24] found that both non-white race and use of MDI (vs CSII) were significantly associated with an increased frequency of DKA events.[24] In contrast, in a study examining a broader adult population (also from the T1D Exchange Clinic Registry), while non-white race was significantly associated with greater frequency of DKA events in a univariate analysis, after adjusting for socioeconomic status, non-white race was no longer a significant predictor of DKA.[13] Similarly, this investigation [13] found no difference in rates of DKA based on insulin delivery method.

Quality assessment of included studies

Regarding the quality of the studies included in this SLR, while each study did have potential limitations that should be considered when interpreting the results (Table 1), most investigations were scored as moderate quality based on an assessment using a standardized tool (the JBI prevalence studies quality assessment tool) (Appendix 4). Nearly all studies included in the SLR were susceptible to potential selection bias in the patient population evaluated. In many cases, this was due to use of a clinic-based registry (such as the T1D Exchange Clinic Registry or the DPV database),[13, 24, 29, 31, 35, 38-40, 42] which may not be representative of a broader population-based cohort of T1D patients; in addition, findings from investigations based on patients recruited from a single center [25, 30, 37, 41, 43, 45] may not be generalizable to a wider group of T1D patients. No studies were identified by this review that utilized an unselected population-based approach to recruit subjects, such as surveys based on population census data.

Many studies included in this SLR did not provide sufficient information to make a clear determination of study quality for some aspects of study design; this lack of detail was particularly notable for ascertainment of cases of T1D. Only two studies [35, 44] included any description of criteria for the diagnosis of T1D. Of these two, the Chinese study [44] refers to American Diabetes Association and World Health Organization guidelines for diagnosis but does not explicitly state the criteria used to determine T1D cases. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult. When insufficient details were provided to permit assessment of a given study quality parameter, the study was given an “unclear” rating for that aspect of study quality.

Regarding the definition or method of determination of DKA events, there was little consensus among the included studies. Several publications (for example, those based on the T1D Exchange Clinic Registry [13, 24, 31, 35, 38-40]) relied on patient recall of past DKA events. Many studies evaluated DKA events as recorded in hospital/medical records (note that some of these studies utilized patient report of hospitalization),[13, 22-24, 29-31, 38-40, 42, 44] while other investigations did not require hospitalization as part of the definition of DKA or suggested the patient required intravenous fluid or insulin infusion without specifically stating a requirement for hospitalization.[25, 43, 45] Interestingly, three publications [13, 24, 31] based on the T1D Exchange Clinic Registry did a direct comparison of frequency of DKA events based on patient self-report vs medical record extraction and, in each case, found that the number of events was higher for patient self-reporting than was captured in the patients' medical records. The authors suggested that DKA may be underreported in clinical records and, therefore, chose to use patient self-reported data for further analyses.

While most studies were rated as having moderate study quality based on the JBI prevalence studies quality assessment checklist (Appendix 4), a few outliers were identified with both high and low quality. Most of the studies that scored highly on the quality assessment [13, 22, 23, 29, 42] did so because they provided additional information and details not available in other publications. For example, a study of the DPV database evaluating the impact of physical activity on diabetes outcomes [29] reported a direct comparison of baseline characteristics of patients included in the analysis and those excluded due to missing data, to rule out a significant impact of selection bias in this study. Similarly, as mentioned above, in Weinstock (2013) [13] the authors included two sets of analyses using data for DKA events based on patient self-report and patients' medical records in an attempt to address the limitation of patient recall in determining the frequency of the DKA outcome. In contrast, studies that received lower quality ratings provided incomplete or conflicting information that made it difficult to evaluate the results.[37, 41, 43] In a

single-center study conducted in Colorado (US),[37] ascertainment of T1D cases and definition of DKA were not reported, the study period and denominator for calculation of prevalence or incidence were unclear, and the sample size was relatively small (515 patients). Likewise, in a single-center cohort study performed in Slovenia,[41] the definitions for T1D cases, DKA events, and denominator for determination of DKA events were not reported, and the study included only 184 patients. In Appendix 4, the notation "Unclear" generally means that insufficient details were provided in the publication to make an informed determination of study quality for that particular question of the JBI assessment tool.

Discussion

Out of 1,082 citations identified, 19 publications met the inclusion and exclusion criteria for this SLR. Over half of the included studies evaluated patient cohorts based in North America [13, 22-24, 31, 35-40]; data were more limited for studies conducted in Europe [29, 30, 41-43] or elsewhere.[25, 44, 45] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[25, 29, 30, 36, 37, 41, 44, 45] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[13, 22-24, 31, 35, 38-40, 42, 43] The lowest incidence rates were reported in Israel and North America [36, 45] and the highest in China [44]. The lowest prevalence was reported in Sweden [43] and the highest in Canada [23] No publications reported both incidence rate and prevalence of DKA. Five studies [22, 23, 30, 37, 41] provided sufficiently detailed information to allow for calculation of one of the outcomes of interest when these measures were not directly reported by the study authors. Several publications reported DKA outcome data stratified by age.[13, 24, 35, 38, 40] In contrast, subgroup data for patients categorized based on other baseline characteristics, such as sex,[13] ethnicity,[13] or insulin delivery method,[13, 38] were scarce. While there was considerable variation in study design and data sources among the studies included in the SLR, the majority of investigations presented recently obtained data (within the previous 10 years), and patient baseline characteristics were broadly similar. Many studies were cross-sectional in design or were

identified as cross-sectional by the study authors, particularly those examining large (>10,000) patient databases [24, 29, 35, 38, 40]; the few studies that followed patients longitudinally tended to be single-center and to have small (<200) sample sizes.[30, 41, 43] Based on the limited available data, prevalence and incidence rates for DKA were broadly similar across geographic regions but did differ for specific subgroups of patients.

Most studies included in this SLR were assessed as being of moderate quality. Nearly all studies in the review were susceptible to potential selection bias in the included patient population or were of limited generalizability. In addition, many included studies did not provide sufficient information to make a clear determination of quality for some aspects of study design; this lack of detail was particularly notable for ascertainment of cases of T1D. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult.

There was little consensus among the included studies regarding the definition of, or method to determine, DKA events. One of the main issues affecting the quality determination for many of the included studies is the fact that the epidemiology of DKA events was not a primary (or, in many cases, even a secondary) objective of the study; rather, DKA data were reported only as part of overall rates of acute diabetic complications (along with other parameters such as severe hypoglycemic events). This may contribute to the lack of detailed descriptions of DKA events. The findings from the Chinese study highlight the difficulties encountered in comparing the epidemiological data across the included studies, in which the methods of calculating incidence rate or prevalence often were not explicitly described. In particular, calculations of incidence rate are challenging without complete information on the patient numerator, given that a single patient can experience multiple recurrent DKA events; it is important to determine whether the

incidence rate refers to the number of discrete episodes of DKA or to the number of patients who experienced a DKA event. Most studies [13, 22-24, 31, 35, 37-43] (13 of 19) reported the percentage of patients who had experienced at least one DKA episode (or two or more episodes [30]) over a given study period, rather than the total number of DKA events. In other cases, data were aggregated as cumulative sums of DKA events during the study period[29] or reported as events per patient per year,[45] and some studies[25, 36, 44, 45] did not provide details regarding the method of calculation of incidence rates.

To our knowledge, this is the first SLR on the epidemiology of DKA in adults with T1D. The strength of this study is the strict delineation that was taken to appropriately assess epidemiology data specifically in adults with T1D. Of note, both young adults and elderly patients were included in this SLR, so the results could be applicable across the whole spectrum of the adult population. Many (24) studies were omitted from the SLR based on the inability to stratify adult data separately from pediatric and/or adolescents or T1D data from a combined diabetic population (T1D and T2D combined).

This review, like any SLR, is subject to limitations that should be considered when interpreting the results. All SLRs are subject to publication bias, as an SLR inherently relies upon data available in the published literature.[34] While a few studies were identified by this SLR that reported findings that did not support one of the authors' primary hypotheses (eg, in Butalia 2014,[23] driving distance to outpatient care was not associated with diabetic outcomes; in Wong 2014,[40] there was no significant association between use of continuous glucose monitoring and DKA events among adult T1D patients), it is likely that null results may be infrequently published. In addition, only data from studies published in English were included in the SLR. This restriction may limit the available data from certain geographic regions in which English is not the primary language of publication and limits the overall scope of the review. As part of the

abstract review process, the authors identified non-English studies (which had English abstracts available for review) and found fewer than 10 studies that had the potential for inclusion in the SLR, with data from Japan, China, Bulgaria, Senegal, and the Ivory Coast. Similarly, studies of fewer than 50 adult patients with T1D were excluded. This restriction was deemed reasonable given the epidemiological outcomes of interest (prevalence and incidence rate), as deriving these values from a very small patient population would lead to a high degree of uncertainty in the estimates. However, it is likely that relevant data for smaller cohorts of patients may not have been included due to this restriction. This SLR was originally intended to include only population-based studies but was expanded to include clinic-based and (potentially unrepresentative) registry studies since there were so few population-based studies found. The small number of studies identified by the review limits the interpretation of comparisons within or between geographic regions and subgroups defined by patient clinical characteristics.

Of note, although the authors acknowledge the availability of nationwide population-based databases with high ascertainment rates in the Nordic countries, which could be used to evaluate epidemiologic queries in T1D, publications on DKA rates among adults in this region were very limited; only one such study [43] met the inclusion criteria for this SLR. Two additional studies of potential interest were identified but ultimately excluded from this review; an epidemiology study based on Denmark public health registries reported the incidence of DKA in the general population and not just among patients with T1D and was thus excluded from the SLR.[46] A study from Sweden reported an incidence rate for DKA of 5.9 per 100,000 adults with T1D but defined adults as ≥15 years of age; since this SLR strictly evaluated patients ≥18 years of age, the study was excluded.[47] Similarly, two additional publications [48, 49] reporting data on DKA incidence or prevalence based on patients in the UK were excluded from this review due to lack of patient demographic information; neither study provided sufficient details to allow determination of the patient age range and therefore may have included data for pediatric T1D

patients. Based on hospital records in Leicestershire, England, [48] the prevalence of DKA could be calculated as 13.7 per 1,000 over the two-year study period. An investigation of T1D patients in Scotland [49] found that the cumulative incidence of DKA events was 154 events per 1,000 for the overall population, with considerable variation based on patients' economic status.

The wide range of incidence rates and prevalence of DKA in adults with T1D [25, 29, 30, 36, 37, 41, 44, 45] is similar to the published literature for children. The incidence of DKA in children with T1D (aged 0–18 years) was lowest in Sweden (15 per 1,000 PY) and highest in the US (80–150 per 1,000 PY; children aged 0–19 years) prior to the Diabetes Control and Complications Trial (DCCT), based on a summary of the epidemiological literature at the time.[50] After raised awareness associated with the DCCT, the incidence of DKA in children with T1D (aged 13–17 years) was 47 per 1,000 PY with conventional therapy vs 28 per 1,000 PY with intensive therapy.[50] Whereas adults with T1D have decreasing prevalence of DKA with increasing age,[13] an opposite relationship may exist in children. In subgroup analyses of children with T1D, incidence of DKA increased with age for girls (40 per 1,000 PY in girls <7 years of age; 80 per 1,000 PY in girls 7–12 years of age; 120 per 1,000 PY in girls ≥13 years of age, $P<0.001$ for trend) but not for boys (70 per 1,000 PY in boys <7 years of age; 50 per 1,000 PY in boys 7–12 years of age; 80 per 1,000 PY in boys ≥13 years of age).[50] This suggests a plateau effect for risk of DKA, particularly in females. Rewers and colleagues[50] indicated that the increased risk of DKA among adolescent girls (relative to younger children) may be related to body image issues that lead adolescent girls to skip insulin injections to promote weight loss. Increased insulin resistance due to puberty or obesity may also play a role in greater risk of DKA, as higher insulin dose was a predictor of DKA (at all ages). Eating disorders, frequent among children with diabetes, also may affect risk of DKA but may be challenging to identify in this population.[50] Similar to adults with T1D,[13] the prevalence of DKA is higher in non-white vs white ethnicities in children. Non-Hispanic black children with T1D have the highest rate of DKA (23%) vs Hispanic

children (12%) and non-Hispanic white children (7%).[51] Also similar to adults,[13] the risk of DKA increases in children with psychiatric disorders, those who are underinsured, and those who have uncontrolled HbA1c.[50] In a study evaluating children in the US, the overall prevalence of DKA at presentation in adolescents (aged 10–19 years) with T2D was 57 per 1,000 and 311 per 1,000 among children and adolescents (aged 0–19 years) with T1D.[52] Among children with T2D, prevalence of DKA at diabetes onset decreased with increasing age, with 73 per 1,000 children 10–14 years of age vs 42 per 1,000 children 15–19 years of age. The relationship between DKA prevalence at diagnosis and age generally was similar among children with T1D; prevalence values were 411 per 1,000 for children aged 0–4 years, 298 per 1,000 for children aged 5–9 years, 309 per 1,000 for adolescents aged 10–14 years, and 235 per 1,000 for older children aged 15–19 years.[52]

Given the above limitations of many of the available publications, there is a clear need for future investigations to better elucidate the epidemiology of DKA among adult patients with T1D. For future studies, it will be important to clearly describe how cases of T1D are identified and to utilize a standardized definition of DKA, as both of these factors are weaknesses of the currently available evidence. Ideally, future studies would focus specifically on DKA outcomes and employ population-based methods to identify T1D patients and would therefore be more representative of a broad, unselected patient population. It would also be advisable to utilize data from some of the existing large, multicenter, clinic-based registries, such as the US-based T1D Exchange Clinic Registry,[13, 24, 31, 35, 38-40], Nordic databases, the Clinical Practice Research Datalink (CPRD) in the UK, and the German/Austrian DPV,[29, 42] to evaluate large cohorts of patients longitudinally to attempt to confirm some of the associations that have been suggested by cross-sectional analyses of these databases and to identify any changes in DKA trends over time. Since 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. In addition, since DKA is a potentially life-threatening complication and there are currently limited data available on the mortality rates of DKA in a general T1D population, the existing large data sources in the US and Europe could be used to describe DKA-related mortality.

Conclusions

This SLR is, to our knowledge, the first review to describe the epidemiology of DKA among adult patients with T1D. The review identified a limited number of relevant studies; most data were from clinic-based registries of selected patient populations, and most patient cohorts were based in North America. Patient subgroup data were very limited, but a general trend was observed for decreasing prevalence of DKA with increasing patient age. Several other factors, such as lower socioeconomic status, poor glycemic control, and depression or psychiatric symptoms, were associated with increased risk of DKA. There is a clear need for future studies to better describe the epidemiology of DKA among adult T1D patients, but from the currently available body of evidence, which provides an overall prevalence of DKA ranging from approximately 50 to 100 events per 1,000, it is clear that there remains an unmet need to address the prevention of this serious complication of T1D among adult patients.

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Contributors: Brett A Maiese (BAM), Erika Wissinger (EW), Soulmaz Fazeli Farsani (SFF) conceived and designed the study. EW and BAM undertook the literature search, assessed

studies for eligibility, and extracted data. In case of disagreement SFF checked the study. BAM, EW, SFF, Kimberly Brodovicz (KB), Nima Soleymanlou (NS), and Jan Marquard (JM) discussed the data, interpreted the results, reviewed the manuscript and revised it critically. NS and JM provided clinical input. All authors approved the final version and take full responsibility for the integrity of the data and the accuracy of the data summarization and interpretation.

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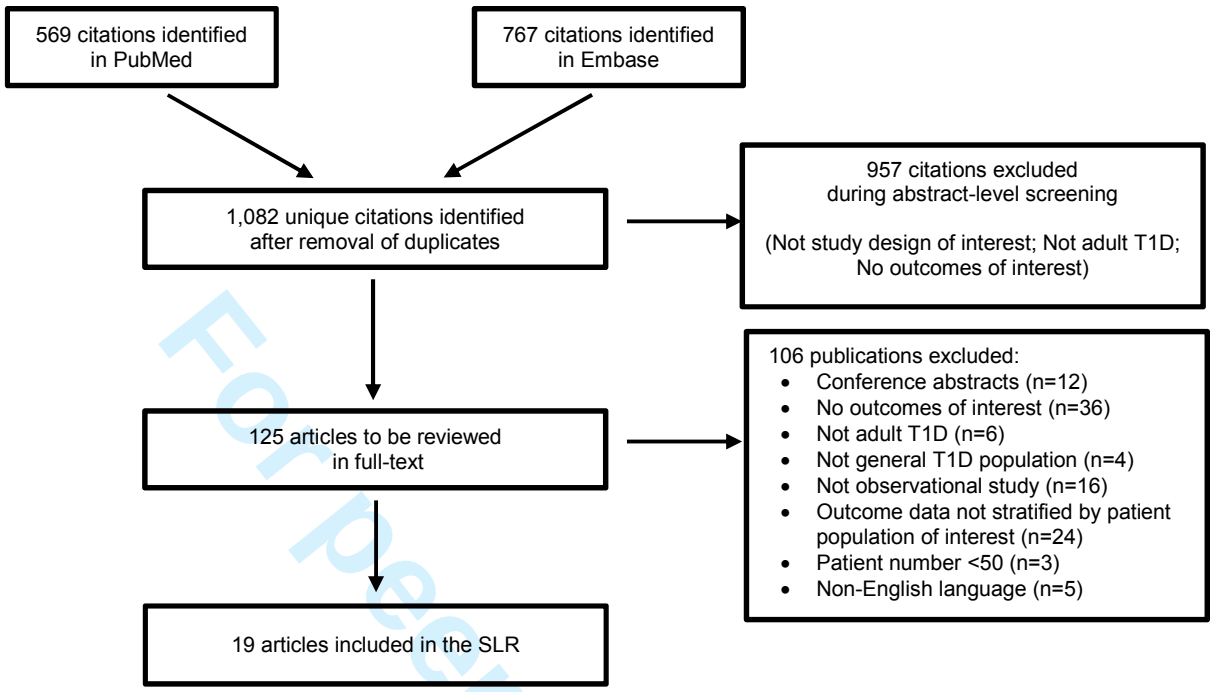
Ethics approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Additional data are available in the appendices.

FIGURES, TABLES, and APPENDICES:

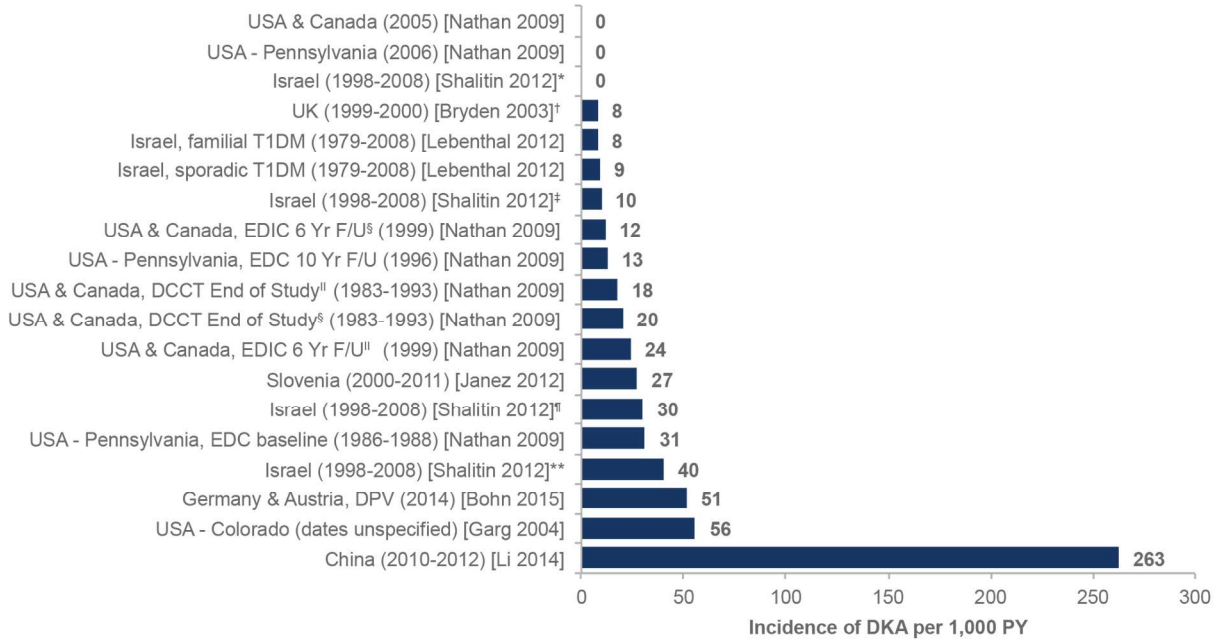
Figure 1. Literature Selection and Review Process



Key: SLR = systematic literature review; T1D = type 1 diabetes mellitus.

Key Search Terms: Type 1 diabetes; adult; diabetic ketoacidosis.

Figure 2. Incidence Rate per 1,000 PY of DKA in Adults With T1D (Reported in 8 Studies)



Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; F/U = follow-up; PY = person-years; T1D = type 1 diabetes mellitus; UK = United Kingdom; USA = United States of America; yr = year.

*Calculated value based on data contained within publication.

†Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at CSII initiation.

‡Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at last visit.

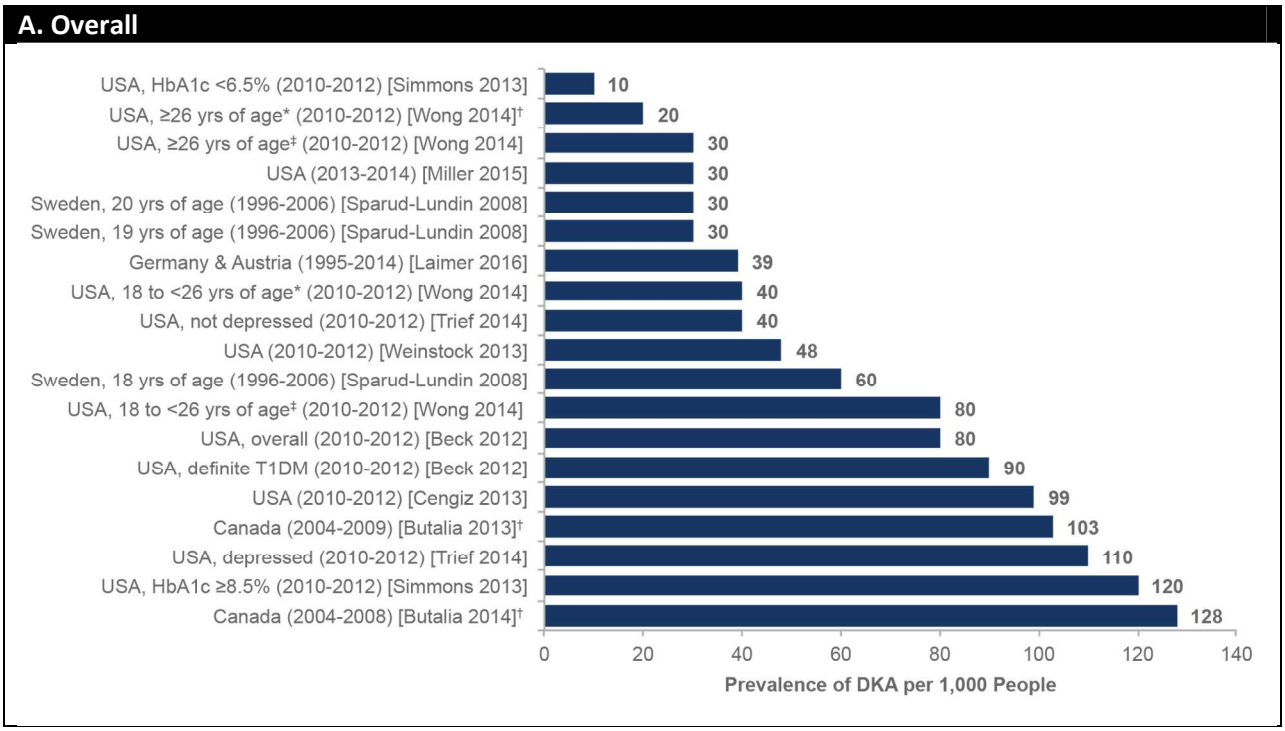
‖Conventional treatment arm from DCCT.

§Intensive treatment arm from DCCT.

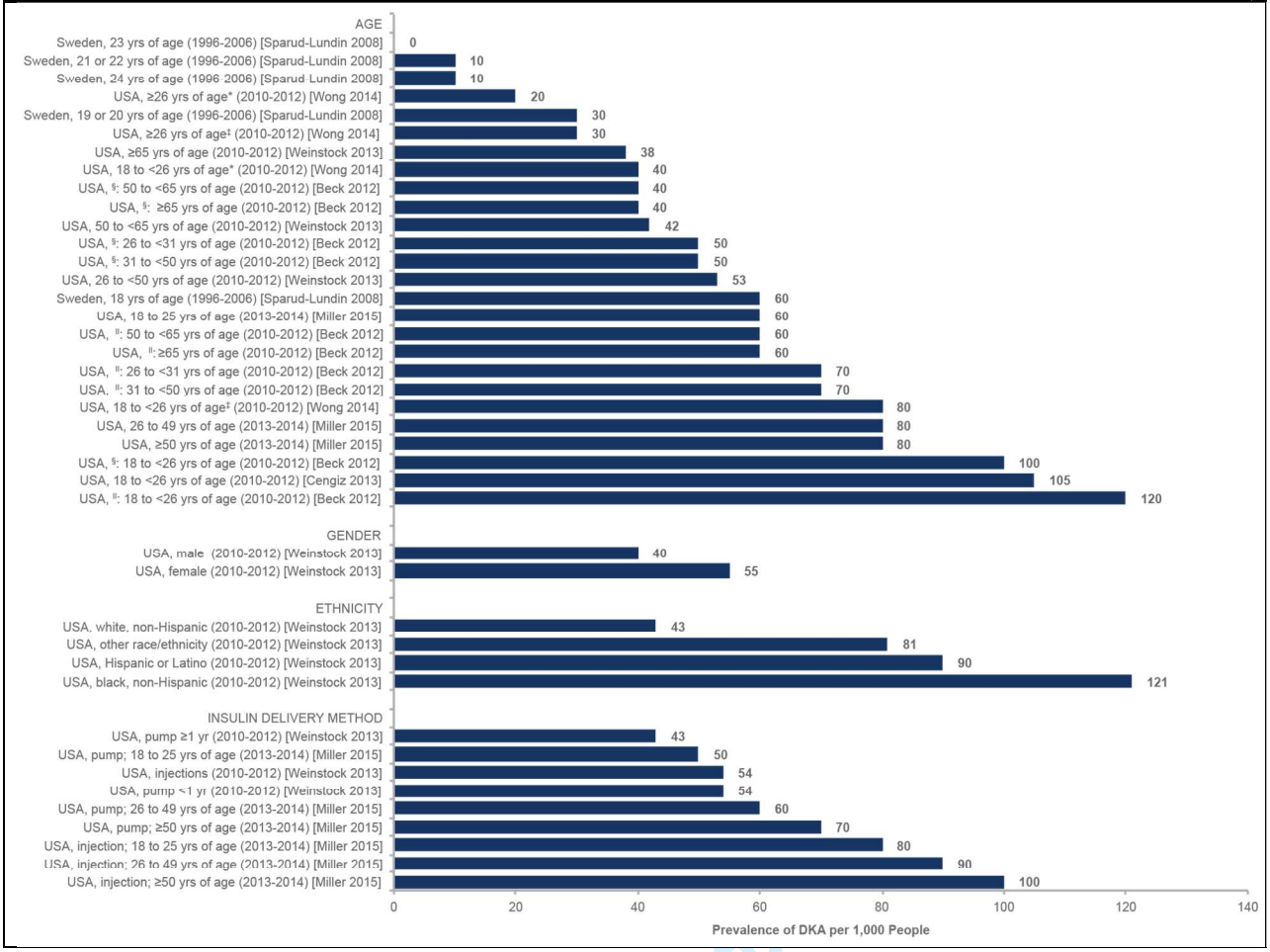
¶Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at CSII initiation.

**Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at last visit.

Figure 3. Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies)



B. By Subgroups of Interest



Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c = glycosylated hemoglobin; MDI = multiple daily injection; NR = not reported; T1D = type 1 diabetes mellitus; yrs = years.

*CGM non-user.

†Calculated value based on data contained within publication.

‡CGM user.

§Overall study population.

‖Definite T1D.

Table 1. Summary of Study Limitations for Studies Reporting Incidence Rate of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Bohn 2015[29] **JBI Score: 9**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all receiving "routine care"	Total population with physical activity data in the DPV	Information bias: low Selection bias: unclear
Bryden 2003[30] **JBI Score: 7**	Longitudinal single-center cohort	NS	89% (initially), with 87 of the 113 patients included at follow-up	All cases were based on hospitalization, likely low	Unclear; patients from 1 specialist care clinic. Only data for patients with recurrent DKA admissions were reported	All follow-up person-time in the cohort	Information bias: low Selection bias: possible
Garg 2004[37] **JBI Score: 1**	Clinic-based single-center registry	NS	N/A (single-center medical record data)	Authors state use of definition from the DCCT Group (unclear potential)†	Unclear; patients all treated at 1 specialty diabetes clinic	Unclear; 515 patients on whom they pulled data	Information bias: low Selection bias: possible
Janez 2012[41] **JBI Score: 0**	Clinic-based single-center registry	NS	N/A (single-center registry/database data)	NS; misclassification potential unclear; data from medical records (not self-report)	Unclear; patients are all treated at 1 specialty diabetes clinic	Unclear; 184 patients on whom they pulled data	Information bias: low Selection bias: possible
Lebenthal 2012[25] **JBI Score: 6**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all from 1 clinical center	Unclear	Information bias: low (but missing data) Selection bias: unclear
Li 2014[44] **JBI Score: 6**	Longitudinal assessment of patients referred from 16 tertiary care hospitals in 1 province	NS	N/A (patient medical records)	Standardized/criteria-based definition, but data on DKA came from questionnaires (unclear potential)	Unclear; patients are all from tertiary hospitals in 1 Chinese province	NS; likely the entire study population	Information bias: unclear Selection bias: unclear

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Nathan 2009[36] **JBI Score: 7**	DCCT/EDIC (initially an RCT; converted almost all patients to a cohort study design); EDC is a cohort study	NS for either DCCT/EDIC or EDC	NS for DCCT, but 96% of trial participants agreed to participate in EDIC NS for EDC	NS for either cohort. The DCCT/EDIC has both self-reported and clinic-measured variables (method of DKA assessment not stated); unclear potential	Initial cohort for DCCT/EDIC was selected for an RCT, increasing likelihood that patients may not reflect the broader T1D population. For EDC, authors state participants were representative of T1D population of Allegheny County, PA	Unclear	Information bias: low Selection bias: low
Shalitin 2012[45] **JBI Score: 6**	Tertiary care university hospital-based study	NS	N/A (single-center patient medical records)	Highly specific definition based on medical records; likely low	Unclear; patients were treated at a specialized tertiary care center	Unclear, but authors state there was up to 7 yrs of follow-up data on patients after CSII initiation	Information bias: low Selection bias: low

Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; JBI = Joanne Briggs Institute; N/A = not applicable; NS = not stated; PA = Pennsylvania; RCT = randomized controlled trial; T1D = type 1 diabetes mellitus; yr = year.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9. In this manuscript, for the purposes of ease of discussion, a descriptive quality rating of "high" was given to studies with 8 or more Yes responses, and a descriptive quality rating of "low" was given to studies with 3 or fewer "Yes" responses. Studies with more than 3 and fewer than 8 "Yes" responses were described as "moderate" quality.

†The study authors cite this source: *N Engl J Med.* 1993 Sep 30;329(14):977-986; however, upon review, the source did not describe definition of DKA in the DCCT, nor did a high-level Internet search.

Table 2. Summary of Study Limitations for Studies Reporting Prevalence of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Beck 2012[35] **JBI Score: 7**	Clinic-based registry	Stratified data provided for patients with confirmed T1D†	Very good	Self-report, potential for misclassification	Patient treated by endocrinologists	All patients in registry during specific study time period	Information bias: yes (past events) Selection bias: possible
Butalia 2013[22] **Butalia 2014**[23] **JBI Score: 8**	Linked database analysis	NS	N/A (used linked database data)	Valid; based on hospitalization	Unclear	Patients in the Diabetes, Hypertension and Cholesterol Centre database (2 centers)	Information bias: low Selection bias: possible
Cengiz 2013[24] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-reported hospitalization)‡	Patients treated by endocrinologists	All patients meeting age and disease duration requirements during study time period	Information bias: yes (past events) Selection bias: possible
Laimer 2016[42] **JBI Score: 9**	Clinic-based registry	NS	N/A (used clinic-based patient data)	Standardized, likely low	Unclear	Unclear why this is such a small subset of the overall DPV database population	Information bias: low Selection bias: unclear
Miller 2015[38] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-report); only reported for prior 3 months	Patients all treated by endocrinologists§	All patients in registry during study period who had DKA data from a web-based questionnaire	Information bias: possible (past events) Selection bias: possible
Simmons 2013[39] **JBI Score: 7**	Clinic-based registry	Not explicitly described in this publication	Not stated in this publication	Likely (self-report)	Patients are all treated by endocrinologists, which may introduce some selection bias	Did not include patients with missing data on type of insulin administration or users of real-time CGM	Information bias: possible (past events) Selection bias: possible

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Sparud-Lundin 2008[43] **JBI Score: 3**	Clinic-based study	Not stated	86% of potential participants were included; 79% longitudinally followed	Relied on pH value, could be misclassified. 11.5% of the DKA values were missing at the latest time point	Patients all treated at 1 pediatric diabetes clinic and then had to be treated at 1 of 6 adult clinics	Unclear, assumed to be age-specific patient groups (not person-time)[‖]	Information bias: low Selection bias: possible
Trief 2014[31] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS; this analysis only includes patients with PHQ-8 data[‖]	Yes (self-reported hospitalization)[‡]; only reported for prior 3 months	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period who had PHQ-8 data	Information bias: possible (past events) Selection bias: possible
Weinstock 2013[13] **JBI Score: 8**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period	Information bias: possible (past events) Selection bias: possible
Wong 2014[40] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during specific study time period	Information bias: possible (past events) Selection bias: possible

Key: CGM = continuous glucose monitoring; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; JBI = Joanna Briggs Institute; N/A = not applicable; NS = not stated; PHQ-8 = Patient Health Questionnaire-8 response; T1D = type 1 diabetes mellitus.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9.

[†]Confirmation of T1D diagnosis was problematic for some adult-onset patients with incomplete clinical data; therefore, this group of patients may include some adults with T2D who were misdiagnosed with T1D.

[‡]The frequency of DKA occurrence reported by the clinics from medical record extraction was lower compared to patients' self-report of DKA events.

[§]The authors mention that "uninsured individuals are likely underrepresented in the cohort and pump use may be higher than it is in the overall population of type 1 diabetes in the US".

[‖]PHQ-8 is an 8-item questionnaire that was given at the 1-year data collection point to participants aged ≥18 years.

Appendix 1. Search Strategy Protocol

Submitted as supplementary file.

Appendix 2. Incidence and Prevalence of DKA

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
US and Canada								
Beck 2012[35]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	25,833*	NR	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 80† Definite T1D: 90
Butalia 2013[22]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, and census in Canada	1,994	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	127.9‡
Butalia 2014[23]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, census, and database of postal codes in Canada	1,467	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	102.9‡
Cengiz 2013[24]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	13,487 DKA subset, n=13,005 Aged 18 to <26 yrs subset, n=3,624	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 99
Garg 2004[37]	Retrospective analysis from a single center	Electronic patient record system in US	515	NR	Patient medical records	Number of patients who had a DKA event over the study period	Cumulative incidence: 55.6‡	NR

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
Miller 2015[38]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	16,061* DKA subset, n=2,561	Participant-reported DKA diagnosed by a doctor that required treatment in a healthcare facility	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Overall: 30
Nathan 2009[36]	Observational, longitudinal cohort study	EDIC study (extension of DCCT in Canada and US) EDC study in US	***Conventional treatment*** DCCT, n=730 EDIC, n=606 ***Intensive treatment*** DCCT, n=711 EDIC, n=620 ***EDC*** Baseline, n=161; Year 10, n=105; Year 18, n=88	NR	NR	Incidence rate per 1,000 PY	***Conventional treatment*** DCCT: 18 EDIC Year 6: 24 EDIC Year 12: 0 ***Intensive treatment*** DCCT: 20 EDIC Year 6: 12 EDIC Year 12: 0 ***EDC*** Baseline: 31 Year 10: 13 Year 18: 9	NR
Simmons 2013[39]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	1,894	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Excellent HbA1c control (<6.5%): 10 Fair/poor HbA1c control (≥8.5%): 120
Trief 2014[31]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	6,172	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Depressed: 110 Non-depressed: 40
Weinstock 2013[13]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	7,012 DKA subset, n=6,796	Patient-reported overnight hospitalization for DKA Clinic-documented hyperglycemia and symptoms such as polyuria, polydipsia,	Patient self-report via questionnaire (these data were used for all primary analyses)	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 48

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
				nausea, or vomiting; serum ketones or large/moderate urine ketones; arterial blood pH <7.30, or venous pH <7.30, or serum bicarbonate <15 mmol/L; and treatment provided in a healthcare facility				
Wong 2014[40]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	17,317*	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	***18 to <26 yrs*** CGM user: 80 CGM non-user: 40 ***≥26 yrs*** CGM user: 30 CGM non-user: 20
Europe								
Bohn 2015[29]	Cross-sectional analysis of prospective, clinic-based patient registry	DPV prospective database of T1D patients in Germany and Austria	18,028	pH value <7.3 or hospital admission due to DKA	Patient medical records	DKA events per 100 PY	51.3	NR
Bryden 2003[30]	Single-center longitudinal cohort study	Case register of a young adult diabetic clinic in United Kingdom	113	Hospital admissions for DKA	Patient medical records	Number of patients with ≥2 admissions for DKA over 1,261 PY of follow-up	7.9‡	NR
Janez 2012[41]	Prospective, single-center, clinic-based patient registry	Registry of adult T1D patients treated with CSII in Slovenia	184	NR	Patient medical records	Number of patients with a DKA episode over the study period	Cumulative incidence: 27.2	NR
Laimer 2016[42]	Cross-sectional analysis of prospective, clinic-based	DPV prospective database of T1D patients in	5,545	Hospital admission due to ketoacidosis with hyperglycemia >11 mmol/L and pH <7.3	Patient medical records	Percentage of patients with a DKA event	NR	39

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
	patient registry	Germany and Austria						
Sparud-Lundin 2008[43]	Single-center, clinic-based longitudinal cohort study	Diabetes outpatient medical/nursing records from age 18–24 yrs in Sweden	104	Blood pH <7.30	Patient medical records	Number and percentage of patients with a DKA event for each year (from 18–24 yrs)	NR	Aged 18: 60 Aged 19: 30 Aged 20: 30 Aged 21: 10 Aged 22: 10 Aged 23: 0 Aged 24: 10
Other Regions								
Lebenthal 2012[25]	Retrospective analysis	Medical records from a single center in Israel	452*	Blood pH <7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	DKA events per 100 PY	Familial T1D: 8 Sporadic T1D: 9	NR
Li 2014[44]	Cross-sectional, multicenter, clinic-based study	Patient medical records from 16 tertiary hospitals in China	611*	Hyperglycemia (blood plasma glucose >13.9 mmol/L), blood bicarbonate <15 mmol/L and/or pH <7.30 (arterial), and elevated level of ketones in the urine or blood	Patient medical records; diagnosis based on criteria of the Chinese Diabetes Society, the American Diabetes Association , Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology	DKA events per 100 PY	263	NR
Shalitin 2012[45]	Retrospective analysis of patient medical records from a single center	Medical records from a single center in Israel ***Group 1:*** CSII initiated within 1 year of diagnosis ***Group 2:*** CSII initiated at least 1 year post-diagnosis	488*	Blood pH < 7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	Average number of DKA events per patient per year	***Group 1*** >19 yrs at last visit: 10 >19 yrs at CSII initiation: 0 ***Group 2*** >19 yrs at last visit: 40 >19 yrs at CSII initiation: 30	NR

Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; DPV = Diabetes-Patienten-Verlaufsdokumentation; ICD-10-CA = International Classification of Diseases, 10th Revision with Canadian Enhancements; NR = not reported; PY = person-years; SLR = systematic literature review; T1D = type 1 diabetes mellitus; US = United States; yrs = years.

* Overall study population; includes pediatric T1D patients (outcome data not included for pediatric patients).

† The overall patient population includes both definite T1D cases (patients meeting all diagnostic criteria) and probable T1D cases (patients meeting only some of the diagnostic criteria); the results for the definite T1D population were reported separately.

‡ Shaded (gray) cells represent outcome data that were calculated by the authors of this SLR based on the information available in the publication, rather than data directly reported by the study authors. Cumulative incidence was calculated/defined as number of cases out of total study population.

Appendix 3. DKA Risk Factors and Associations

Reference	Methods	Measures of DKA Association/Risk	Comments
Bohn 2015[29]	Multiple Poisson regression models adjusted for age, sex, and diabetes duration, with treatment center as a random factor provided adjusted estimates of the incidence of DKA events per 100 PY: mean (standard error)	Adjusted estimate of DKA events per 100 PY: mean (standard error) Inactive patients (n=11,357): 6.48 (0.03) Patients who were physically active 1–2 times per week (n=3459): 3.99 (0.03) Patients who were physically active >2 times per week (n=3212): 2.40 (0.03)	**A significant inverse association was found between rates of DKA and level of physical activity** for the overall study population and for all subgroups (all *P*<0.0001)
Bryden 2003[30]	Multiple and logistic regression analyses with dependent variables: psychiatric referral, recurrent DKA admissions over the study period, any serious diabetic complication, HbA1c, and psychiatric symptoms at follow-up Independent variables entered into the model at baseline were sex, psychiatric symptoms, HbA1c, duration of diabetes, BMI, number of daily injections, and marital status Sex and baseline psychiatric symptoms were forced into the model, but other covariates that were not statistically significant at the 10% level were excluded from final models	Presence vs absence of psychiatric symptoms at baseline: **OR: 9.1; 95% CI: 2.9 to 28.6; *P*<0.0001** for recurrent admissions for DKA	**Patients with recurrent admissions for DKA over the study period were significantly more likely to have developed diabetic complications at follow-up than patients without recurrent DKA admissions**, and in multiple regression analyses, recurrent admissions for DKA over the study period predicted psychiatric symptoms at follow-up
Butalia 2013[22]	Logistic regression was used to calculate simple bivariate ORs for the associations between the DKA outcome and individual predictor variables. This was then followed by multivariable logistic regression modelling, for which backward elimination was performed to construct a parsimonious prediction model Variable elimination was carried out in thematic groups: the healthcare system, socioeconomic status, comorbidities, diabetes complications, indicators of complications, BMI, age, and sex	In univariate analyses, DKA hospitalization was associated with: Younger age **OR: 0.98 per year; 95% CI: 0.97 to 0.99** Lower BMI **OR: 0.94; 95% CI: 0.92 to 0.97** Shorter duration of T1D **OR: 0.97 per year; 95% CI: 0.96 to 0.98** Use of statin medications lowered the risk of DKA hospitalization **OR: 0.60; 95% CI: 0.42 to 0.86** Several comorbidities and complications were associated with increased risk of DKA hospitalization: Gastroparesis **OR: 3.85; 95% CI: 1.90 to 7.89** Psychiatric diagnosis **OR: 1.90; 95% CI: 1.21 to 2.97** Increased eGFR **OR: 1.12 per 10 mL/min 1.73 m^2; 95% CI: 1.06 to 1.17** Higher HbA1c **OR: 1.29 per 1% increase; 95% CI: 1.20 to 1.39** was associated with DKA hospitalization Higher quartiles of income compared with the lowest quartile (quartile 2, **OR: 0.66; 95% CI: 0.46 to 0.96**; quartile 3, **OR: 0.66; 95% CI: 0.45 to 0.95**; quartile 4: **OR 0.8; 95% CI: 0.68 to 0.96**) and more formal education (**OR: 0.42; 95% CI: 0.18 to 0.97**) lowered the odds of DKA hospitalization In multivariable logistic regression, longer duration of T1D was associated with lower odds of DKA hospitalization (**OR: 0.96 per year; 95% CI: 0.95 to 0.98**). Other factors significantly associated with DKA hospitalization included gastroparesis (**OR: 4.13; 95% CI: 1.82 to 9.35**), psychiatric diagnosis (**OR: 1.98; 95% CI: 1.22 to 3.19**), and higher HbA1c (**OR: 1.25; 95% CI: 1.16 to 1.35**)	

Reference	Methods	Measures of DKA Association/Risk	Comments
Butalia 2014[23]	Multivariate logistic regression analyses were used to assess the association between driving distance from patient residence to outpatient diabetes care sites and the DKA outcome Unadjusted and adjusted models for clinical and sociodemographic factors also were constructed for DKA hospitalization. Clinical factors included BMI, duration of diabetes, specialist care, comorbidities and complications, HbA1c, and eGFR. Other variables included sex, age, median family income, and neighborhood education level (proportion with university degree/diploma/certificate)	In multivariate analyses, driving distance from home to diabetes center 1 (adjusted OR: 1.02 per 1 km; 95% CI: 0.96 to 1.07) to diabetes center 2 (adjusted OR: 1.01; 95% CI: 0.99 to 1.04) or to closest general practitioner (adjusted OR: 0.9; 95% CI: 0.63 to 1.25) was not associated with DKA hospitalization	Patients with DKA hospitalization were younger, had shorter duration of T1D, and had higher HbA1c than patients without DKA hospitalization
Cengiz 2013[24]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01. Interactions among age, diabetes duration, sex, and HbA1c were evaluated, and no interaction term was significant at the level of 0.01	Detailed data on OR for adjusted and unadjusted models and numerous patient stratifications are available in Table 3 and Supplemental Table 2 of the publication	After adjusting for age, a higher **frequency of DKA was significantly associated with female sex, non-white race, lower income, no private insurance, higher HbA1c, and MDI insulin method (vs pump); (all *P*<0.001).** In a multivariate analysis**, female sex, higher HbA1c, non-white race, lower income, and lack of private insurance continued to be significantly associated with a higher frequency of DKA**. Results were similar for each age group.
Laimer 2016[42]	Linear regression analysis adjusted for age, sex, duration of diabetes, and basal insulin rate per kg body weight was used to analyze the association between basal rate variability and DKA	In male adult T1D patients, a **higher variability index of basal insulin rates was associated with higher frequency of DKA (r=0.04; *P*=0.029)** Logistic regression analysis (adjusted for age, sex, duration of disease, and total basal insulin) **confirmed significant positive correlations of the variability index of basal insulin rates with DKA (β=0.012; *P*=0.017) and between basal insulin rates (basal rate/kg/24h) and DKA (β=1.743; *P*<0.001),** but not with age (β=0.008; *P*=0.159), duration of disease (β=0.001, *P*=0.884), or sex (β=0.205, *P*=0.154) and DKA	
Lebenthal 2012[25]	Multiple logistic regression by stepwise backward methods was applied to determine variables significantly associated with acute complications	Overall rates of DKA events were significantly higher in familial than in sporadic cases (2.8 vs 1.9 events per 100 PY) **IRR=1.5; 95% CI: 1.03 to 2.22; *P*=0.03** Note that this association was not significant for patients aged >19 years (IRR=0.92 [95% CI: 0.36 to 2.32], *P*=0.87)	A higher mean HbA1c level was a predictor for DKA events in both the familial and the sporadic groups, whereas age at diagnosis of T1D and sex did not predict DKA events in either group
Li 2014[44]	A Poisson regression model was used to determine risk factors for secondary DKA. Separate backwards stepwise logistic regression analyses were used to identify risk factors for the recurrence of secondary DKA	Detailed data on relative risk are available in Figure 1 of the publication and results of logistic regression analyses for secondary DKA recurrence are reported in Table 2 For the overall population, the following parameters were	There were no significant differences in DKA incidence between patients treated with insulin glargine and patients treated with NPH insulin

Reference	Methods	Measures of DKA Association/Risk	Comments
		significant risk factors for secondary DKA: Female sex (**RR=2.12; 95% CI: 1.50 to 3.04**) Medical reimbursement rates <50% (**RR=1.84; 95% CI: 1.33 to 2.60**) Uncontrolled diet ("never controlled" vs "usually controlled") (**RR=1.76; 95% CI: 1.18 to 2.57**) Smoking (**RR=2.18; 95% CI: 1.30 to 3.59**) Poor glycemic control (HbA1c per1.0% increase, **RR=1.15; 95% CI: 1.10 to 1.21**) An overweight/obese BMI (vs normal) significantly reduced the risk of secondary DKA (**RR=0.57; 95% CI: 0.31 to 0.96**) In logistic regression models, recurrence of secondary DKA was associated significantly with: Female sex (**RR=10.56; 95% CI: 1.97 to 56.72; *P*=0.01**) Smoking (**RR=6.99; 95% CI: 1.02 to 48.00; *P*=0.05**) Poor β cell function (stimulated C-peptide/100 pmol/L decrease (**RR=4.22; 95% CI: 1.20 to 6.97; *P*=0.01**) Poor glycemic control (HbA1c per1.0% increase, (**RR=1.16; 95% CI: 1.00 to 1.34; *P*=0.05**)	Regarding recurrences, 34.4% of secondary DKA episodes represented recurrent events (≥2 episodes) in 3.8% of the patients
Miller 2015[38]	No statistical modelling analyses reported; qualitative summary data only	NR	The frequency of DKA tended to be higher among participants with higher HbA1c levels and slightly lower among participants using an insulin pump
Shalitin 2012[45]	No statistical modelling analyses reported; summary data only based on Pearson's chi-square test or Fisher's exact test	NR	The rates of DKA episodes were not significantly different between the 2 groups (patients who initiated CSII within 1 year of diagnosis or patients who initiated CSII at least 1 year after diagnosis), either in total or on subanalysis by age groups, pubertal stages, diabetes duration, or CSII treatment duration
Trief 2014[31]	Diabetes-management outcomes (including DKA) in those with and without depression were compared using linear regression for continuous variables and logistic regression models for categorical variables	Compared with non-depressed participants, depressed participants had more frequent DKA events in the past 3 months (**11% vs 4%; *P*<0.001** for all 3 definitions of depression) Compared with lower-scoring participants, participants with higher depression scores were more likely to experience more frequent DKA (***P*<0.001)** NR	

Reference	Methods	Measures of DKA Association/Risk	Comments
Weinstock 2013[13]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01	Detailed data on OR and 95% CI from logistic regression models evaluating the association between baseline demographic and clinical characteristics and the occurrence of a patient-reported or clinic-reported DKA event are described for numerous patient subgroup stratifications in Table 2 and Supplemental Table 3 of the publication	Frequency of DKA was lower with increasing age. However, the age effect was largely explained by HbA1c level, which was strongly associated with the occurrence of a DKA event. Frequency of DKA was not associated with diabetes duration In addition to HbA1c level, **a higher frequency of DKA was associated with lower socioeconomic status based on education level, income, and insurance status (*P*<0.001 for each in multivariate model) and female sex (*P*=0.008)**. In univariate models, non-Hispanic black and Hispanic participants had higher frequencies of DKA than non-Hispanic whites, and current smokers had higher frequency of DKA than nonsmokers, but after adjusting for socioeconomic status, neither factor was significant in the multivariate model. Frequency of DKA was not significantly different between pump and injection users
Wong 2014[40]	Logistic regression modelling adjusted for sex, race/ethnicity, education level, annual household income, health insurance status, diabetes duration, and insulin delivery method (pump/ injection)	CGM UYser vs CGM non-user: <u>18 to <26 yrs:</u> Unadjusted OR: 0.5; 95% CI: 0.2 to 1.0; *P*=0.06 Adjusted OR: 0.6; 95% CI: 0.2 to 1.8; *P*=0.33 <u>≥26 yrs:</u> Unadjusted OR: 0.7; 95% CI: 0.4 to 1.1; *P*=0.09 Adjusted OR: 1.4; 95% CI: 0.8 to 2.3; *P*=0.23	CGM use was not significantly associated with rates of DKA for these age groups in logistic regression models

Key: BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin A1c; IRR = incidence rate ratio; NPH = neutral protamine Hagedorn; NR = not reported; OR = odds ratio; PY = person-years; RR = relative risk; T1D = type 1 diabetes mellitus.

Bold text highlights associations that were found to be statistically significant in each study.

* Associations were calculated based on the full patient population (which included pediatric patients); however, analyses were adjusted for age.

Appendix 4. Quality Assessment of Included Studies (JBI Prevalence Studies Checklist)

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview N=21 studies	**12 (57%) Yes 7 (33%) Unclear 2 (10%) No**	**17 (81%) Yes 3 (14%) Unclear 1 (5%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**18 (86%) Yes 0 (0%) Unclear 3 (14%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**9 (43%) Yes 12 (57%) Unclear 0 (0%) No**	**11 (52%) Yes 9 (43%) Unclear 1 (5%) No**	**18 (86%) Yes 3 (14%) Unclear 0 (%) No**	**16 (76%) Yes 4 (19%) Unclear 1 (5%) No**
Beck 2012[35]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Bohn 2015[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bryden 2003[30]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2013[22]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2014[23]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cengiz 2013[24]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Garg 2004[37]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Janez 2012[41]	No	No	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear
Laimer 2016[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lebenthal 2012[25]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear
Li 2014[44]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Miller 2015[38]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Nathan 2009[36]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Shalitin 2012[45]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview N=21 studies	**12 (57%) Yes 7 (33%) Unclear 2 (10%) No**	**17 (81%) Yes 3 (14%) Unclear 1 (5%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**18 (86%) Yes 0 (0%) Unclear 3 (14%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**9 (43%) Yes 12 (57%) Unclear 0 (0%) No**	**11 (52%) Yes 9 (43%) Unclear 1 (5%) No**	**18 (86%) Yes 3 (14%) Unclear 0 (%) No**	**16 (76%) Yes 4 (19%) Unclear 1 (5%) No**
Simmons 2013[39]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Sparud-Lundin 2008[43]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Trief 2014[31]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Weinstock 2013[13]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Wong 2014[40]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Key: JBI = Joanna Briggs Institute.

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Study protocol: Systematic Literature Review of the Incidence and Prevalence of Diabetic Ketoacidosis among Adults with Type 1 Diabetes

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1.0 INTRODUCTION

Diabetic ketoacidosis (DKA) is a potentially lethal complication of type 1 diabetes (T1D), resulting in up to 30% mortality of all hospitalized cases and attributing up to 76% of all diabetes-related deaths.

Although the epidemiology of DKA in T1D has been well characterized in pediatric patients, the incidence and prevalence of DKA has not been established in adults with T1D.

Boehringer Ingelheim (BI) GmbH seeks to better understand the available published data describing the incidence and prevalence of DKA in adults with T1D, including any relevant epidemiological data reported for stratified patient subgroups (such as by age, gender, geographic location, ethnicity, or typical method of insulin administration). To achieve this, Xcenda will perform a systematic literature review (SLR) which will follow the processes outlined within this study protocol.

The purpose of this protocol is to prospectively define the specific parameters by which the SLR of the incidence and prevalence of DKA in adults with T1DM will be conducted. This systematic literature review will follow the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Any changes made after agreement may impact the final research findings, associated project fees, and timeline. A change log of protocol amendments is located in Appendix A.

2.0 KEY RESEARCH QUESTIONS

This study will seek to answer the following key question and related query:

1. What is the overall incidence and prevalence of DKA in adult patients (≥ 18 years, including elderly patients) with T1DM?
    a. What is the incidence and prevalence of DKA in adult T1DM patients by subgroups (when reported in the manuscript and if possible to determine), including: age, gender, geographic location, ethnicity, type of insulin administration (insulin pumps versus injections)?

3.0 SEARCH STRATEGY

The overall approach to the search is outlined below. Additional features of the search strategy and search terms are further detailed in Section 5.0.

3.1 Data Sources

- MEDLINE (via PubMed)
- Embase

3.2 Search Filters and Limitations

3.2.1 Timeframe

- Studies published between January 1, 2000 and the date of the search will be included

3.2.2 Language and Countries

- Language: English only[1]

[1] Articles that appear relevant but are not published in English will be noted during screening and citations will be provided to BI for review.

- Geography: no geographic limitations will be applied, but areas of greatest interest include North and South America, Europe, Japan, Taiwan, and Australia.

3.2.3 Humans

- Only studies conducted in humans will be identified by the search.

3.2.4 Publication Status

- Published studies will be considered; conference abstracts will not be included in the review.

4.0 STUDY SELECTION CRITERIA

4.1 Population

- Adult (≥18 years) patients with T1DM
    - Elderly patients will be included
    - Studies of mixed populations (pediatric and adult, and/or type 1 and type 2 diabetes) will be included if stratified data are reported for adult T1DM patients. These publications will be categorized in a separate table.

4.2 Interventions/Comparators

The SLR will include all T1DM patients, regardless of treatment. Type of insulin and route of administration are of particular interest and will be captured when these data are available in the literature.

4.3 Outcomes

- Study endpoints (for overall patient population and relevant subgroups)
    - Incidence of DKA
    - Prevalence of DKA

4.4 Study Design

Included study designs:

- Population-based observational studies
- SLRs and meta-analyses[2]

Excluded study designs:

- Randomized controlled trials / clinical trials
- Pharmacokinetic and pharmacodynamic studies
- Non-randomized interventional studies
- Preclinical or animal studies
- Editorials, letters, and commentaries

[2] Reference lists of SLRs will be hand-searched for any articles that may have been missed by the database search. If additional studies are identified (published from 2000 onwards), the data from those studies will be extracted separately. Data extraction for SLRs will only include a basic summary of the study design and overall results.

- Case studies, reports, or case series
- Theses and dissertations
- Narrative literature reviews
- Small studies (n<50)
- Guidelines

5.0 SEARCH TERMS

Table 5-1 outlines the search terms to be considered as well as specific details on the search strategy.

Table 5-1. Search Strategy (with Sample Searches in MEDLINE and Embase)

Database	MEDLINE (via PubMed)	
Search Limitations or Filters Applied	Publication dates: 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	(((((((diabetes mellitus, type 1[MeSH Terms]) OR type 1 diabetes[Title/Abstract]) OR juvenile onset diabetes[Title/Abstract]) OR brittle diabetes[Title/Abstract]) OR insulin dependent diabetes[Title/Abstract]) OR iddm[Title/Abstract]) OR autoimmune diabetes[Title/Abstract]) OR sudden onset diabetes[Title/Abstract]	85,033
#2	(((diabetic ketoacidosis[MeSH Terms]) OR diabetic ketoacidosis) OR diabetic acidosis) OR diabetic ketosis	8,267
#3	((((adult[MeSH Terms]) OR adult) OR young adult) OR middle age) OR elderly	6,589,216
#4	#1 AND #2 AND #3	1,265
#5	review NOT (systematic OR (meta AND analys*))	2,372,581
#6	#4 NOT #5	1131
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**596**

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	'diabetes mellitus, type 1'/exp OR 'type 1 diabetes mellitus':ab,ti OR 'juvenile onset diabetes':ab,ti OR 'brittle diabetes':ab,ti OR 'insulin dependent diabetes':ab,ti OR iddm:ab,ti OR 'autoimmune diabetes':ab,ti OR 'sudden onset diabetes':ab,ti	106,633
#2	'diabetic ketoacidosis'/exp OR 'diabetic acidosis'/exp OR 'diabetic ketosis'/exp	9,093

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#3	'adult'/exp OR 'young adult'/exp OR 'middle age'/exp OR 'elderly'/exp	6,066,920
#4	#1 AND #2 AND #3	1,078
#5	review NOT (systematic OR (meta AND analys*))	3,002,962
#6	#4 NOT #5	950
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**766**

6.0 DATA EXTRACTION

Data extraction will be conducted in MS Excel and converted into MS Word tables for the final report. The elements for data extraction are outlined in Table 6-1.

Table 6-1. Example Data Extraction Templates

Author, year	Country	Type of study	Study period	Definition of DKA	Guidelines used for defining DKA	T1DM cases were identified based on?	Study participants				
							Mean, median, and range of age (as available)	Male%	Inclusion/ exclusion criteria	Sample size	Ethnicity

Author, year	Type of insulin	Insulin pump (Y/N)	Follow up years	N of new cases of DKA	Denominator for calculating rates of DKA	INC of DKA per 1000 PY	PREV of DKA per 1000 people	Conclusions	Notes/Comments/study limitations

APPENDIX A: PROTOCOL CHANGE LOG

Date	Protocol Section	Amendment	Status
Date of change	*Section X*	*Description of change*	*Completed Y/N*

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-14; Figs 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 1 & 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

BMJ Open

Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review

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Keywords:	EPIDEMIOLOGY, DIABETES & ENDOCRINOLOGY, PUBLIC HEALTH

Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review

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ABSTRACT

OBJECTIVES

To summarize incidence and prevalence of diabetic ketoacidosis (DKA) in adults with type 1 diabetes (T1D) for the overall patient population and different subgroups (age, sex, location, ethnicity, and type of insulin administration).

DESIGN

Systematic literature review (SLR)

DATA SOURCES

MEDLINE (via PubMed) and Embase (1 January 2000 to 23 June 2016).

STUDY SELECTION

Peer-reviewed observational studies with reported data on the incidence or prevalence of DKA in T1D adults were included. A single reviewer completed the study screening and selection process and a second reviewer screened additionally approximately 20% of the publications; two reviewers independently conducted the quality assessment; the results were narratively synthesized.

RESULTS

Out of 1,082 articles, 19 met the inclusion and exclusion criteria, with two additional studies identified that did not specify the patient age range and are therefore not included in the SLR. Overall, eight studies reported incidence with a range of 0–56 per 1,000 person-years (PYs), with one outlying study reporting an incidence of 263 per 1,000 PYs and 11 studies reporting prevalence with a range of 0–128 per 1,000 people. Prevalence of DKA decreased with increasing age. Based on data from no more than two studies per subgroup, there was a higher prevalence of DKA reported in women than men, in non-white than white ethnic groups, and in patients treated with insulin injections than those using continuous subcutaneous insulin infusion pumps.

CONCLUSIONS

To our knowledge, this is the first SLR on the epidemiology of DKA in T1D adults. Despite an increasing prevalence of T1D in recent years, DKA in adults has been poorly characterized. In an era when the benefit-risk profiles of new antidiabetic therapies are being evaluated, including the potential risk of DKA, there is a clear need to better elucidate the expected rate of DKA among T1D adults.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- To our knowledge, this is the first literature review to systematically assess and summarize the incidence rate and prevalence of DKA in adults with T1D.
- Both young adults and the elderly were included in this SLR, so the results may be applicable across a wide spectrum of adult T1D patients.
- The quality of included studies was assessed using a standardized tool (the JBI prevalence studies quality assessment tool).
- This review, like any SLR, is subject to publication bias, as an SLR inherently relies upon data available in the published literature.
- Studies not published in English were excluded from the SLR, as were studies of fewer than 50 patients.

KEY WORDS: diabetic ketoacidosis; type 1 diabetes mellitus; systematic literature review; incidence; prevalence; epidemiology;

Introduction

Diabetes is a disease characterized by high blood glucose resulting from abnormal insulin production, function, or both.[1] Type 1 diabetes mellitus (T1D) develops when insulin-producing beta cells in the pancreas are destroyed.[1] This destruction is modulated by the body's immune system and leads to a limitation in, or complete cessation of, the production and secretion of insulin, which results in the need for external insulin delivery in order to survive.[1] T1D typically follows an acute clinical course, with patients presenting with polyuria, polydipsia, and weight loss.[2] According to the International Diabetes Federation (IDF), approximately 542,000 children 0−14 years of age have T1D, with 86,000 new cases diagnosed worldwide each year.[3] While there are geographical differences, the overall annual increase in the incidence of T1D is estimated at approximately 3%−4%.[3, 4] Diagnosis of T1D typically occurs in childhood; in the United States (US), the peak age at diagnosis is approximately 14 years. Compared to adults without the disease, patients with T1D at age 20 years have an estimated loss of life expectancy of approximately 13 years for women and 11 years for men.[5, 6]

Information regarding the epidemiology of T1D specifically in adults is scarce; many epidemiological studies of adult patients categorize those with blood glucose levels above a certain threshold as simply diabetic, without providing more detailed data on the relative proportions of patients with T1D versus type 2 diabetes mellitus (T2D).[3] Approximately 5% of adult-diagnosed cases of diabetes are diagnosed as T1D,[1] although an Italian study has shown rates of T1D as high as 50% of incident cases of diabetes among normal-weight adults (aged 30−54 years).[7] Incidence of T1D varies by age and is reported to be 9.0−61.7 per 100,000 in the US, 4.9−6.7 per 100,000 in Austria, 9.4−55.0 per 100,000 in Sweden, 12.2 per 100,000 in the UK, 15.9 per 100,000 in Finland, and 22−38.2 per 100,000 in Sardinia.[8-11] A recent systematic literature review (SLR) reported the incidence of T1D to be 1.5 times higher in males than in females less than 40 years of age.[8]

Diabetic ketoacidosis (DKA) is a major acute metabolic complication of T1D that is typically marked by acidosis, ketosis, and usually hyperglycemia.[12-14] Diabetic ketoacidosis is diagnosed in different ways, but typically the following three factors are present: elevated plasma glucose (>250 mg/dL), ketones in serum or urine, and acidosis (serum bicarbonate <18 mEq/L and/or pH <7.30).[12] The symptoms of uncontrolled diabetes that may lead to development of DKA are typically of short duration and include polyuria, polydipsia, polyphagia, weight loss, vomiting, abdominal pain, weakness, and drowsiness.[12, 14] Management of DKA includes fluid and electrolyte therapy, insulin therapy, treatment of any identified triggering causes (eg, pump failure, sepsis, pneumonia, acute pancreatitis, cerebrovascular accident, myocardial infarction, stroke, trauma, medications that affect carbohydrate metabolism), and monitoring of therapy and resultant complications.[12, 14, 15] Excessively rapid fluid resuscitation should be avoided to prevent cerebral edema, a rare but debilitating and potentially fatal complication of DKA.[12] While inpatient mortality rates for DKA are generally very low (<1% in Scotland [16] and in the US [17]), rates vary substantially based on healthcare setting; a recent analysis conducted in India reported that up to 30% of hospitalized DKA cases result in inpatient death.[15] Among all T1D-related deaths for patients aged less than 30 years, 54%–76% can be attributed to DKA.[18-21] Risk factors associated with a higher frequency of DKA may include younger age at time of DKA hospitalization,[22, 23] higher mean glycosylated hemoglobin A1c (HbA1c),[13, 22-25] infection,[26] continuous subcutaneous insulin infusion (CSII) pump failure,[27, 28] lower socioeconomic status/household income,[13, 22, 24] lower physical activity level,[29] and psychiatric symptoms/depression.[22, 30, 31] The prevalence of DKA at initial disease presentation in pediatric T1D patients is well documented [32, 33]; however, information on the prevalence or incidence in adults is limited. One study using the T1D Exchange Clinic Registry in the US found that 4.8% of participants reported one or more DKA events (requiring self-reported overnight hospitalization) in the previous 12 months.[13] The objectives of this SLR were to summarize the

available epidemiological data (incidence rate and prevalence) for DKA in adult patients (aged ≥18 years) with T1D from population-based and other observational studies and to evaluate trends in the evidence for the overall patient population and specific subgroups (age, sex, geography, ethnicity, and type of insulin administration such as CSII or multiple daily injections [MDIs]).

Methods

Search strategy and selection process

This systematic review was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[34] The Study protocol (including search strategy and search terms) was developed and accepted by all authors prior to commencement of the search and can be found in Appendix 1. MEDLINE (via PubMed) and Embase databases were searched for articles published between January 1, 2000 and June 23, 2016 (date of search execution) by a single review author (EW). The searches were filtered for human studies, but no language restrictions or geographic limitations were applied to the search strategy. Note that only studies published in English were included. Relevant studies published in other languages were noted during screening and a list of these citations reviewed for consideration. Included studies were peer-reviewed, and ongoing studies without peer-reviewed publication (eg conference abstracts) were excluded. The search results were combined in a referencing software database, and duplicate records were removed.

Upon second-pass review, a single review author (EW or BAM) applied the following criteria. The targeted population was males and females aged at least 18 years with T1D. When sufficient data were available in the publications to permit determination of the patients' age range (for example, mean age and standard deviation [SD] or standard error), the relevant calculations were performed to determine eligibility for inclusion (for example, mean age ± three

SD as an estimate of the range of study patients' age). If the mean age was reported and the calculated age for minus three SDs was <18 years, the study was excluded, unless the study population was explicitly described as adults aged ≥18 years. Studies of mixed populations (pediatric and adult patients and/or T1D and T2D) were included only if stratified data were reported for adult T1D patients. This review was not restricted by specific interventions or comparators and included all T1D patients, regardless of treatment. 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. Type of insulin and method of administration were of interest and were captured when these data were available. Peer-reviewed population-based observational studies, SLRs, and meta-analyses of human studies were included. This SLR was originally intended to include only population-based studies but was expanded to include other observational study designs such as clinic-based and (potentially unrepresentative) registry studies since there were so few population-based studies found. Because the aim of the review was to assess real-world epidemiology outcomes reported in the peer-reviewed literature describing studies of humans, randomized controlled trials/clinical trials and interventional studies were excluded, as were preclinical or animal studies, editorials, letters, commentaries, case studies, reports or case series, theses and dissertations, narrative literature reviews, small studies (sample size of fewer than 50 patients), guidelines, and unpublished studies (eg, conference abstracts).

Data extraction and analysis

Data extraction was conducted by a single review author (EW or BAM) using a Microsoft® Excel file with standardized definitions for each data element that was extracted from each study (see Appendix 1). Clinical outcomes of interest were incidence rate of DKA (number of new DKA events out of accumulated patient time under study, in person-years [PYs]) and prevalence of DKA (number of DKA events among the total number of patients at risk). Data on risk factors

and clinical parameters associated with DKA events were also extracted when reported in the included publications. When sufficient data were available in the published literature to allow computation of these outcomes if not specifically reported by the authors (for example, the number or proportion of patients who experienced a DKA event over a defined time period), the appropriate calculations were performed and are noted as such. For two publications, cumulative incidence was calculated (number of new DKA events out of total patients at risk) because data on incidence rates were not directly reported in the publications. Results from data extraction, including incidence rate, prevalence, and risk factors for DKA, can be found in Appendices 2 and 3.

The quality of included studies was assessed by a trained epidemiologist (BAM), with consideration of the study design, disease ascertainment, response rate (if applicable), definition of DKA, representativeness of the study population, and major potential biases. A table describing these factors for each included study can be found in this report (Table 1). Additionally, a standardized quality assessment tool, the Joanna Briggs Institute (JBI) Critical Appraisal Tools "Checklist for Prevalence Studies" (available at http://joannabriggs.org/research/critical-appraisal-tools.html), was selected as an appropriate tool for assessment of the included study designs. Quality assessment of each included study using the JBI Checklist for Prevalence Studies was undertaken independently by two reviewers (EW and BAM), with any discrepancies resolved by a third reviewer (Xcenda employee, member of evidence synthesis team). The results of the quality assessment using the JBI tool can be found in Appendix 4.

Patient involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. No patients were asked to advise on

interpretation or reporting of results. There are no plans to disseminate the results of the research to patient communities.

Results

Figure 1 summarizes the literature review process, including the number of records identified, the screening and eligibility results, and the final list of included references. Out of 1,082 articles identified through the initial search, 19 peer-reviewed observational study publications met the inclusion and exclusion criteria; no SLRs or meta-analyses were identified that met the inclusion and exclusion criteria. There were 11 publications in North America (US and Canada),[13, 22-24, 31, 35-40] five publications in Europe,[29, 30, 41-43] and three publications in Israel or China.[25, 44, 45] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[25, 29, 30, 36, 37, 41, 44, 45] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[13, 22-24, 31, 35, 38-40, 42, 43] The lowest incidence rates were reported in Israel and North America (both 0 events per 1,000 PYs)[36, 45] and the highest in China (263 events per 1,000 PYs)[44] (Figure 2). The lowest prevalence was reported in Sweden (0 per 1,000 people)[43] and the highest in Canada (127.9 per 1,000 people)[23] (Figure 3a).

In terms of baseline characteristics, patient selection, and descriptions of outcomes, there were some broad similarities across studies included in this review. In most studies, specific definitions or diagnostic criteria for T1D were not described, and some studies did not fully report patient baseline demographic information such as patient ethnicity or insulin delivery method. Standardized measurements of DKA events were not frequently utilized, as many studies (seven of 19) relied on patient self-report of DKA episodes or hospitalization records (four of 19). Three publications[13, 24, 31] based on data from the T1D Exchange Clinic registry directly compared DKA data based on patient self-reported and clinic-documented events and found that, while the frequency of participant-reported DKA events was higher than clinic-

reported events based on medical records, results from logistic regression models designed to assess potential associations with DKA episodes were similar for both sets of data.[13] Few exclusion criteria were applied to the patient populations, most commonly pregnancy and lack of available data. The age range of patient cohorts varied across studies, with some investigations (two of 19) restricted to young adults only (approximately 18–26 years of age), four studies focused on adults aged approximately 20–55 years, and most (12 studies) evaluating adults of all ages, including those aged over 65 years. Most (16 of 19) studies had approximately a 1:1 male-to-female ratio of patients. Ethnicity of the patient cohorts was only reported in eight studies; when reported, the vast majority of patients (>80%) were of white non-Hispanic ethnicity. In the publications providing data on insulin delivery method in unselected populations (11 of 19 studies), most (50%–60%) patients were treated with CSII. While the number of studies providing data on insulin delivery method was limited, there seemed to be an overall trend toward an increasing proportion of CSII users in more recent publications/study periods compared with older investigations.

Overall incidence and prevalence of DKA in North America

Eleven studies conducted in North America (US and Canada) reported incidence rate (2) or prevalence (9) for DKA events in adults with T1D (Appendix 2). Results from two long-term observational cohorts found that the incidence of DKA showed a general reduction over time, with an incidence rate of approximately 20 cases per 1,000 PYs at baseline to 0 events at the 12-year follow-up in one cohort and a decrease from approximately 30 cases per 1,000 PYs at baseline to <10 cases per 1,000 PYs at the 18-year follow-up in another cohort.[36] A US-based study from a single clinic in Colorado compared CSII pump users (42% of patients) to patients treated with MDIs (58% of patients) [37]; over the study period of approximately 1 year, only patients treated with CSII experienced any DKA events. In this investigation, the cumulative incidence of DKA was calculated to be 55.6 per 1,000 people for CSII users.

All of the publications describing prevalence of DKA in the US were based on data from the T1D Exchange Clinic Registry, although each investigation evaluated a slightly different patient population. All of these studies relied on patient self-report to determine occurrence of DKA events, and the recall period varied from three to 12 months. For most studies of the larger patient population from the registry, prevalence ranged from approximately 50 to 100 per 1,000 people.[13, 24, 35, 40] Slightly higher DKA prevalence than that reported in the US-based studies was observed in two analyses of Canadian data using the following databases: Diabetes, Hypertension, and Cholesterol Center in Calgary, Alberta Inpatient Discharge Abstract Database, Alberta Kidney Disease Network, and Statistics Canada 2006 Census Data.[22, 23] In these linked database studies, calculated prevalence was found to be 103 per 1,000 people [23] and 128 per 1,000 people.[22] These Canadian studies relied on linked data from hospital inpatient admissions rather than patient self-report.

Overall incidence and prevalence of DKA in Europe

In very broad terms, the incidence rates and prevalence reported for European studies (Appendix 2) were similar to those described in investigations conducted in North America; however, these trends should be considered with substantial caution given the very small number of European publications reporting each outcome. Only five publications described the epidemiology of DKA in adult patient populations in Europe; two reported on patients from the Diabetes-Patienten-Verlaufsdokumentation (DPV) database, which includes patients in Germany and Austria [29, 42]; and three evaluated small single-center patient cohorts.[30, 41, 43] In all cases, DKA events were ascertained based on patient medical records.

Incidence rates ranged from approximately 8 cases per 1,000 PYs (calculated rate based on hospital admissions for DKA) in a study of 113 young adults in Oxfordshire, England [30] to 51.3

cases per 1,000 PYs (reported rate based on pH <7.3 or hospital admission for DKA) for over 18,000 adult patients selected from the DPV database.[29] A Slovenian single-center study of patients treated with CSII [41] provided sufficient data to calculate cumulative incidence of 27.2 cases per 1,000, a lower value than that observed in a similar US-based study (55.6 per 1,000).[37] It should be noted that while the study period was unclear in the US investigation, based on publication date (2004 for the US study), it is likely that the Slovenian study (with a study period through 2011) included more recent data. This may have had an impact on DKA results given the technological improvements in insulin pumps and glucose monitoring over this period; indeed, the US study reported that the majority of DKA events recorded were due to pump malfunctions.

Prevalence of DKA was reported in two European studies.[42, 43] One single-center longitudinal study of 104 patients performed in Sweden [43] found a numerical (but not statistically significant) reduction in DKA cases with increasing year of age from 18 to 24 years (prevalence ranged from 0 to 60 cases per 1,000 people over this period). A cross-sectional analysis of patients from the DPV database examining the association of variability in basal insulin rates with various outcomes reported the prevalence of DKA as 39 cases per 1,000 people,[42] also a slightly lower value than the prevalence data reported for US- or Canadian-based studies.

Overall incidence of DKA in other regions

Three studies conducted in other regions reported only incidence rate data (Appendix 2), with very low rates observed in two studies based on patient medical records from the same tertiary care facility in Israel [25, 45] and very high rates described in a multicenter study conducted in tertiary care units in a single province in China.[44] The low incidence rates in the Israeli studies (ranging from 0 to 40 cases per 1,000 PY) may reflect some selection bias in the patient population treated at this single center.[25, 45] In the Chinese study,[44] the authors acknowledge

that the incidence rate observed in their study (263 per 1,000 PY) is considerably higher than values cited in published reports from other countries. The investigators attribute this discrepancy, at least in part, to differences in national healthcare systems, which may limit access to routine healthcare for some T1D patients in China, as well as infrequent self-monitoring of blood glucose by patients and inappropriate treatment or errors in diabetes management. Although not explicitly described in the publication, it seems likely that this study reported the incidence rate of all DKA events during the study period, rather than only the first instance of DKA for each patient. The authors stated that in this study, more than a third (34.4%) of DKA events represented recurrent (two or more) episodes of DKA for 3.8% of patients, suggesting that a small population of very high-risk patients contributed substantially to the overall incidence rate.

DKA prevalence by age

Five publications from the US-based T1D Exchange Clinic Registry [13, 24, 35, 38, 40] reported prevalence of DKA among adults with T1D with outcome data stratified by age (Figure 3b). Four of the studies examined a broad sample of adult patients aged 18 to >90 years; one analysis [24] focused solely on young adults. Given the design of the registry, all five studies relied on patient self-report of past DKA events; three publications [13, 24, 35] examined the prior 12-month period and two [38, 40] queried patients about the previous three months. There was a general trend of decreasing DKA prevalence with increasing age observed across most studies providing age-stratified data. Young adults (aged 18 years to 25 years) had the highest prevalence of DKA (100−120 cases per 1,000 in studies with 12-month recall and 40−80 cases per 1,000 in studies with three-month recall), while the elderly (aged ≥65 years) had the lower prevalence of DKA (38−60 cases per 1,000 in studies with 12-month recall). The only exception to this trend was a study in which prevalence of DKA was similar across all three adult age ranges (18−25 years, 26−49 years, and ≥50 years).[38] The DKA data in this particular investigation may have been

affected by the study requirement that all patients had an annual follow-up visit at which HbA1c was measured and the shorter duration of recall for DKA events (three months). There was no information on incidence rate stratified by patient age reported in any studies identified by this SLR.

DKA prevalence by other patient subgroups of interest

Subgroup data for patients categorized according to clinical or demographic characteristics other than age, such as sex, ethnicity, insulin delivery method, glycemic control, and depression comorbidity were very limited, with data available from only 1 or 2 studies. As with patient stratification by age, only data on DKA prevalence were available for the other categorical variables reviewed. Based on these limited data, higher prevalence of DKA was observed for women vs men, non-white vs white ethnicities, depressed vs non-depressed patients, patients with fair/poor vs excellent glycemic control, and patients treated with insulin injections compared to those using CSII (Figure 3b).[13, 31, 38, 39]

In a single study designed to investigate cross-sectional associations between patient characteristics and DKA events,[13] female patients had a higher prevalence of DKA over the previous 12-month period than male patients (55 vs 40 cases per 1,000 people, respectively). This study also reported a prevalence of DKA in white non-Hispanic patients of 43 per 1,000, while all other ethnicities had considerably higher prevalence of DKA, ranging from 81 per 1,000 (other race/ethnicity) to 121 per 1,000 (black non-Hispanic) during the same study period.[13] Higher prevalence of DKA was observed among depressed patients (110 per 1,000 for patients with at least one DKA event in the previous three months) than non-depressed patients (40 per 1,000 for patients with at least one DKA event in the previous three months).[31]

DKA was more prevalent in patients with fair or poor glycemic control, defined as HbA1c ≥8.5% (120 per 1,000 for patients with at least one DKA event in the previous 12 months).[39] In contrast, the lowest prevalence of DKA was reported for patients with excellent glycemic control, defined as HbA1c <6.5% (10 per 1,000 for patients with at least one DKA event in the prior 12 months).[39] Patients treated with CSII had lower prevalence of DKA than did patients using injectable insulin.[13, 38] This trend was seen across multiple age groups in one study.[38] However, duration of treatment with a CSII may affect prevalence of DKA, as data for patients who had recently (within the prior year) initiated pump therapy had similar rates of DKA to participants treated with insulin injections (both groups had 54 events per 1,000), and the lower DKA prevalence (43 events per 1,000) was observed only in patients who had been treated with a CSII for at least the previous year.[13] It should be noted that these numerical trends did not demonstrate a statistically significant difference between insulin delivery groups in this study.

DKA risk factors and associations

Over half of the included studies (13 publications) reported at least some data on risk factors or patient characteristics associated with DKA events [13, 22-25, 29-31, 38, 40, 42, 44, 45] (Appendix 3). Almost all of these investigations utilized multiple regression analyses to evaluate the associations between baseline parameters and risk of DKA, adjusted for potential confounding factors such as age, sex, body mass index (BMI), and duration of diabetes.[13, 22-25, 29-31, 38, 42, 44] Two of the studies that investigated risk factors associated with DKA only provided qualitative summaries of the associations.[38, 45]

Several studies identified patient characteristics that were significantly associated with increased risk of DKA.[13, 22, 24, 25, 38, 44] The most frequently reported parameters correlating with DKA events were higher HbA1c/poor glycemic control,[13, 22, 24, 25, 38, 44] lower socioeconomic status (based on income, formal education, and private insurance or some combination

thereof),[13, 22, 24, 44] depression/psychiatric symptoms or diagnosis at baseline,[22, 30, 31] and female sex.[13, 24, 44] Regarding the patient subgroups of interest, some conflicting data were presented for the relationship between DKA events and ethnicity or insulin delivery method. In a population restricted to young adults only (aged 18 years to 25 years) from the T1D Exchange Clinic Registry, Cengiz and colleagues [24] found that both non-white race and use of MDIs (vs CSII) were significantly associated with an increased frequency of DKA events.[24] In contrast, in a study examining a broader adult population (also from the T1D Exchange Clinic Registry), while non-white race was significantly associated with greater frequency of DKA events in a univariate analysis, after adjusting for socioeconomic status, non-white race was no longer a significant predictor of DKA.[13] Similarly, this investigation [13] found no difference in rates of DKA based on insulin delivery method.

Quality assessment of included studies

Regarding the quality of the studies included in this SLR, while each study did have potential limitations that should be considered when interpreting the results (Table 1), most investigations were scored as moderate quality based on an assessment using a standardized tool (the JBI prevalence studies quality assessment tool) (Appendix 4). Nearly all studies included in the SLR were susceptible to potential selection bias in the patient population evaluated. In many cases, this was due to use of a clinic-based registry (such as the T1D Exchange Clinic Registry or the DPV database),[13, 24, 29, 31, 35, 38-40, 42] which may not be representative of a broader population-based cohort of T1D patients; in addition, findings from investigations based on patients recruited from a single center [25, 30, 37, 41, 43, 45] may not be generalizable to a wider group of T1D patients. No studies were identified by this review that utilized an unselected population-based approach to recruit subjects, such as surveys based on population census data.

Many studies included in this SLR did not provide sufficient information to make a clear determination of study quality for some aspects of study design; this lack of detail was particularly notable for ascertainment of cases of T1D. Only two studies [35, 44] included any description of criteria for the diagnosis of T1D. Of these two, the Chinese study [44] refers to American Diabetes Association and World Health Organization guidelines for diagnosis but does not explicitly state the criteria used to determine T1D cases. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult. When insufficient details were provided to permit assessment of a given study quality parameter, the study was given an "unclear" rating for that aspect of study quality.

Regarding the definition or method of determination of DKA events, there was little consensus among the included studies. Several publications (for example, those based on the T1D Exchange Clinic Registry [13, 24, 31, 35, 38-40]) relied on patient recall of past DKA events. Many studies evaluated DKA events as recorded in hospital/medical records (note that some of these studies utilized patient report of hospitalization),[13, 22-24, 29-31, 38-40, 42, 44] while other investigations did not require hospitalization as part of the definition of DKA or suggested the patient required intravenous fluid or insulin infusion without specifically stating a requirement for hospitalization.[25, 43, 45] Interestingly, three publications [13, 24, 31] based on the T1D Exchange Clinic Registry did a direct comparison of frequency of DKA events based on patient self-report vs medical record extraction and, in each case, found that the number of events was higher for patient self-reporting than was captured in the patients' medical records. The authors suggested that DKA may be underreported in clinical records and, therefore, chose to use patient self-reported data for further analyses.

While most studies were rated as having moderate study quality based on the JBI prevalence studies quality assessment checklist (Appendix 4), a few outliers were identified with both high and low quality. Most of the studies that scored highly on the quality assessment [13, 22, 23, 29, 42] did so because they provided additional information and details not available in other publications. For example, a study of the DPV database evaluating the impact of physical activity on diabetes outcomes [29] reported a direct comparison of baseline characteristics of patients included in the analysis and those excluded due to missing data, to rule out a significant impact of selection bias in this study. Similarly, as mentioned above, in Weinstock (2013) [13] the authors included two sets of analyses using data for DKA events based on patient self-report and patients' medical records in an attempt to address the limitation of patient recall in determining the frequency of the DKA outcome. In contrast, studies that received lower quality ratings provided incomplete or conflicting information that made it difficult to evaluate the results.[37, 41, 43] In a single-center study conducted in Colorado (US),[37] ascertainment of T1D cases and definition of DKA were not reported, the study period and denominator for calculation of prevalence or incidence were unclear, and the sample size was relatively small (515 patients). Likewise, in a single-center cohort study performed in Slovenia,[41] the definitions for T1D cases, DKA events, and denominator for determination of DKA events were not reported, and the study included only 184 patients. Given the limited data identified in the published literature on the epidemiology of DKA in adults with T1D, even studies that received lower quality ratings were included in this review, to present the totality of the available evidence. In Appendix 4, the notation "Unclear" generally means that insufficient details were provided in the publication to make an informed determination of study quality for that particular question of the JBI assessment tool.

Discussion

Of the 1,082 citations identified, 19 publications met the inclusion and exclusion criteria for this SLR. Over half of the included studies evaluated patient cohorts based in North America [13, 22-24, 31, 35-40]; data were more limited for studies conducted in Europe [29, 30, 41-43] or elsewhere.[25, 44, 45] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[25, 29, 30, 36, 37, 41, 44, 45] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[13, 22-24, 31, 35, 38-40, 42, 43] The lowest incidence rates were reported in Israeli and North American studies [36, 45] and the highest in a Chinese study.[44] The lowest prevalence was reported in a Swedish study [43] and the highest in a Canadian study.[23] No publications reported both incidence rate and prevalence of DKA. Five studies [22, 23, 30, 37, 41] provided sufficiently detailed information to allow for calculation of one of the outcomes of interest when these measures were not directly reported by the study authors. Several publications reported DKA outcome data stratified by age.[13, 24, 35, 38, 40] In contrast, subgroup data for patients categorized based on other baseline characteristics, such as sex,[13] ethnicity,[13] or insulin delivery method,[13, 38] were scarce. While there was considerable variation in study design and data sources among the studies included in the SLR, the majority of investigations presented recently obtained data (within the previous 10 years), and patient baseline characteristics were broadly similar. Many studies were cross-sectional in design or were identified as cross-sectional by the study authors, particularly those examining large (>10,000) patient databases [24, 29, 35, 38, 40]; the few studies that followed patients longitudinally tended to be single-center and to have small (<200) sample sizes.[30, 41, 43] Based on the limited available data, prevalence and incidence rates for DKA were broadly similar across geographic regions but did differ for specific subgroups of patients.

Most studies included in this SLR were assessed as being of moderate quality. Nearly all studies in the review were susceptible to potential selection bias in the included patient population or were of limited generalizability. In addition, many included studies did not provide sufficient information to make a clear determination of quality for some aspects of study design;

this lack of detail was particularly notable for ascertainment of cases of T1D. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult.

There was little consensus among the included studies regarding the definition of, or method to determine, DKA events. One of the main issues affecting the quality determination for many of the included studies is the fact that the epidemiology of DKA events was not a primary (or, in many cases, even a secondary) objective of the study; rather, DKA data were reported only as part of overall rates of acute diabetic complications (along with other parameters such as severe hypoglycemic events). This may contribute to the lack of detailed descriptions of DKA events. The findings from the Chinese study highlight the difficulties encountered in comparing the epidemiological data across the included studies, in which the methods of calculating incidence rate or prevalence often were not explicitly described. In particular, calculations of incidence rate are challenging without complete information on the patient numerator, given that a single patient can experience multiple recurrent DKA events; it is important to determine whether the incidence rate refers to the number of discrete episodes of DKA or to the number of patients who experienced a DKA event. Most studies [13, 22-24, 31, 35, 37-43] (13 of 19) reported the percentage of patients who had experienced at least one DKA episode (or two or more episodes [30]) over a given study period, rather than the total number of DKA events. In other cases, data were aggregated as cumulative sums of DKA events during the study period[29] or reported as events per patient per year,[45] and some studies[25, 36, 44, 45] did not provide details regarding the method of calculation of incidence rates.

To our knowledge, this is the first SLR on the epidemiology of DKA in adults with T1D. The strength of this study is the strict delineation that was taken to appropriately assess

epidemiology data specifically in adults with T1D. Of note, both young adults and elderly patients were included in this SLR, so the results could be applicable across the whole spectrum of the adult population. Many (24) studies were omitted from the SLR based on the inability to stratify adult data separately from pediatric and/or adolescents or T1D data from a combined population of patients with T1D and T2D.

This review, like any SLR, is subject to limitations that should be considered when interpreting the results. All SLRs are subject to publication bias, as an SLR inherently relies upon data available in the published literature.[34] While a few studies were identified by this SLR that reported findings that did not support one of the authors' primary hypotheses (eg, in Butalia 2014,[23] driving distance to outpatient care was not associated with diabetic outcomes; in Wong 2014,[40] there was no significant association between use of continuous glucose monitoring and DKA events among adult T1D patients), it is likely that null results may be infrequently published. In addition, only data from studies published in English were included in the SLR. This restriction may limit the available data from certain geographic regions in which English is not the primary language of publication and limits the overall scope of the review. As part of the abstract review process, the authors identified non-English studies (which had English abstracts available for review) and found fewer than 10 studies that had the potential for inclusion in the SLR, with data from Japan, China, Bulgaria, Senegal, and the Ivory Coast. Similarly, studies of fewer than 50 adult patients with T1D were excluded. This restriction was deemed reasonable given the epidemiological outcomes of interest (prevalence and incidence rate), as deriving these values from a very small patient population would lead to a high degree of uncertainty in the estimates. However, it is likely that relevant data for smaller cohorts of patients may not have been included due to this restriction. This SLR was originally intended to include only population-based studies but was expanded to include clinic-based and (potentially unrepresentative) registry studies since there were so few population-based studies found. The

small number of studies identified by the review limits the interpretation of comparisons within or between geographic regions and subgroups defined by patient clinical characteristics.

Of note, although the authors acknowledge the availability of nationwide population-based databases with high ascertainment rates in the Nordic countries, which could be used to evaluate epidemiologic queries in T1D, publications on DKA rates among adults in this region were very limited; only one such study [43] met the inclusion criteria for this SLR. Two additional studies of potential interest were identified but ultimately excluded from this review; an epidemiology study based on Denmark public health registries reported the incidence of DKA in the general population and not just among patients with T1D and was thus excluded from the SLR.[46] A study from Sweden reported an incidence rate for DKA of 5.9 per 100,000 adults with T1D but defined adults as ≥15 years of age; since this SLR strictly evaluated patients ≥18 years of age, the study was excluded.[47] Similarly, two additional publications [48, 49] reporting data on DKA incidence or prevalence based on patients in the UK were excluded from this review due to lack of patient demographic information; neither study provided sufficient details to allow determination of the patient age range and therefore may have included data for pediatric T1D patients. Based on hospital records in Leicestershire, England, [48] the prevalence of DKA could be calculated as 13.7 per 1,000 over the two-year study period. An investigation of T1D patients in Scotland [49] found that the cumulative incidence of DKA events was 154 events per 1,000 for the overall population, with considerable variation based on patients' economic status.

The wide range of incidence rates and prevalence of DKA in adults with T1D [25, 29, 30, 36, 37, 41, 44, 45] is similar to the published literature for children. The incidence of DKA in children with T1D (aged 0–18 years) was lowest in Sweden (15 per 1,000 PY) and highest in the US (80–150 per 1,000 PY; children aged 0–19 years) prior to the Diabetes Control and Complications Trial (DCCT), based on a summary of the epidemiological literature at the time.[50] After raised

awareness associated with the DCCT, the incidence of DKA in children with T1D (aged 13–17 years) was 47 per 1,000 PY with conventional therapy compared to 28 per 1,000 PY with intensive therapy.[50] Whereas adults with T1D have decreasing prevalence of DKA with increasing age,[13] an opposite relationship may exist in children. In subgroup analyses of children with T1D, incidence of DKA increased with age for girls (40 per 1,000 PY in girls <7 years of age; 80 per 1,000 PY in girls 7–12 years of age; 120 per 1,000 PY in girls ≥13 years of age, *P*<0.001 for trend) but not for boys (70 per 1,000 PY in boys <7 years of age; 50 per 1,000 PY in boys 7–12 years of age; 80 per 1,000 PY in boys ≥13 years of age).[50] This suggests a plateau effect for risk of DKA, particularly in females. Rewers and colleagues[50] indicated that the increased risk of DKA among adolescent girls (relative to younger children) may be related to body image issues that lead adolescent girls to skip insulin injections to promote weight loss. Increased insulin resistance due to puberty or obesity may also play a role in greater risk of DKA, as higher insulin dose was a predictor of DKA at all ages. Eating disorders, frequent among children with diabetes, also may affect risk of DKA but may be challenging to identify in this population.[50] In one study using the Diabetes Audit and Research in Tayside Scotland (DARTS) database, it was suggested that poor adherence to insulin treatment in young adults with insulin-dependent diabetes mellitus (IDDM) is the major factor that contributes to long-term poor glycemic control and diabetic ketoacidosis.[51]

Similar to adults with T1D,[13] the prevalence of DKA is higher in non-white versus white ethnicities in children. Non-Hispanic black children with T1D have the highest rate of DKA (23%) compared to Hispanic children (12%) and non-Hispanic white children (7%).[52] Also similar to adults,[13] the risk of DKA increases in children with psychiatric disorders, those who are underinsured, and those who have uncontrolled HbA1c.[50]

Given the above limitations of many of the available publications, there is a clear need for future investigations to better elucidate the epidemiology of DKA among adult patients with T1D. For

future studies, it will be important to clearly describe how cases of T1D are identified and to utilize a standardized definition of DKA, as both of these factors are weaknesses of the currently available evidence. Ideally, future studies would focus specifically on DKA outcomes and employ population-based methods to identify T1D patients and would therefore be more representative of a broad, unselected patient population. It would also be advisable to utilize data from some of the existing large, multicenter, clinic-based registries, such as the US-based T1D Exchange Clinic Registry,[13, 24, 31, 35, 38-40], Nordic databases, the Clinical Practice Research Datalink (CPRD) in the UK, and the German/Austrian DPV,[29, 42] to evaluate large cohorts of patients longitudinally to attempt to confirm some of the associations that have been suggested by cross-sectional analyses of these databases and to identify any changes in DKA trends over time. Since 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. In addition, since DKA is a potentially life-threatening complication and there are currently limited data available on the mortality rates of DKA in a general T1D population, the existing large data sources in the US and Europe could be used to describe DKA-related mortality.

Conclusions

This SLR is, to our knowledge, the first review to describe the epidemiology of DKA among adult patients with T1D. The review identified a limited number of relevant studies; most data were from clinic-based registries of selected patient populations, and most patient cohorts were based in North America. Patient subgroup data were very limited, but a general trend was observed for decreasing prevalence of DKA with increasing patient age. Several other factors, such as lower socioeconomic status, poor glycemic control, and depression or psychiatric

symptoms, were associated with increased risk of DKA. There is a clear need for future studies to better describe the epidemiology of DKA among adult T1D patients. From the currently available body of evidence, which provides an overall prevalence of DKA ranging from approximately 50 to 100 events per 1,000, it is clear that there remains an unmet need to address the prevention of this serious complication of T1D among adult patients.

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Contributors: Brett A Maiese (BAM), Erika Wissinger (EW), Soulmaz Fazeli Farsani (SFF) conceived and designed the study. EW and BAM undertook the literature search, assessed studies for eligibility, and extracted data. In case of disagreement SFF checked the study. BAM, EW, SFF, Kimberly Brodovicz (KB), Nima Soleymanlou (NS), and Jan Marquard (JM) discussed the data, interpreted the results, reviewed the manuscript and revised it critically. NS and JM provided clinical input. All authors approved the final version and take full responsibility for the integrity of the data and the accuracy of the data summarization and interpretation.

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FIGURES, TABLES, and APPENDICES:

Figure 1. Literature Selection and Review Process

Submitted as image.

Footnotes:

Key: SLR = systematic literature review; T1D = type 1 diabetes mellitus.

Key Search Terms: Type 1 diabetes; adult; diabetic ketoacidosis.

Figure 2. Incidence Rate per 1,000 PY of DKA in Adults With T1D (Reported in 8 Studies)

Submitted as image.

Footnotes:

Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; F/U = follow-up; PY = person-years; T1D = type 1 diabetes mellitus; UK = United Kingdom; USA = United States of America; yr = year.

*Calculated value based on data contained within publication.

†Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at CSII initiation.

‡Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at last visit.

‖Conventional treatment arm from DCCT.

§Intensive treatment arm from DCCT.

¶Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at CSII initiation.

**Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at last visit.

Figure 3. Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies)

Submitted as image.

Footnotes:

Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c = glycosylated hemoglobin; MDI = multiple daily injection; NR = not reported; T1D = type 1 diabetes mellitus; yrs = years.

*CGM non-user.

†Calculated value based on data contained within publication.

‡CGM user.

§Overall study population.

‖Definite T1D.

Table 1. Summary of Study Limitations for Studies Reporting Incidence Rate of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Bohn 2015[29] **JBI Score: 9**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all receiving "routine care"	Total population with physical activity data in the DPV	Information bias: low Selection bias: unclear
Bryden 2003[30] **JBI Score: 7**	Longitudinal single-center cohort	NS	89% (initially), with 87 of the 113 patients included at follow-up	All cases were based on hospitalization, likely low	Unclear; patients from 1 specialist care clinic. Only data for patients with recurrent DKA admissions were reported	All follow-up person-time in the cohort	Information bias: low Selection bias: possible
Garg 2004[37] **JBI Score: 1**	Clinic-based single-center registry	NS	N/A (single-center medical record data)	Authors state use of definition from the DCCT Group (unclear potential)†	Unclear; patients all treated at 1 specialty diabetes clinic	Unclear; 515 patients on whom they pulled data	Information bias: low Selection bias: possible
Janez 2012[41] **JBI Score: 0**	Clinic-based single-center registry	NS	N/A (single-center registry/database data)	NS; misclassification potential unclear; data from medical records (not self-report)	Unclear; patients are all treated at 1 specialty diabetes clinic	Unclear; 184 patients on whom they pulled data	Information bias: low Selection bias: possible
Lebenthal 2012[25] **JBI Score: 6**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all from 1 clinical center	Unclear	Information bias: low (but missing data) Selection bias: unclear
Li 2014[44] **JBI Score: 6**	Longitudinal assessment of patients referred from 16 tertiary care hospitals in 1 province	NS	N/A (patient medical records)	Standardized/criteria-based definition, but data on DKA came from questionnaires (unclear potential)	Unclear; patients are all from tertiary hospitals in 1 Chinese province	NS; likely the entire study population	Information bias: unclear Selection bias: unclear

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Nathan 2009[36] **JBI Score: 7**	DCCT/EDIC (initially an RCT; converted almost all patients to a cohort study design); EDC is a cohort study	NS for either DCCT/EDIC or EDC	NS for DCCT, but 96% of trial participants agreed to participate in EDIC NS for EDC	NS for either cohort. The DCCT/EDIC has both self-reported and clinic-measured variables (method of DKA assessment not stated); unclear potential	Initial cohort for DCCT/EDIC was selected for an RCT, increasing likelihood that patients may not reflect the broader T1D population. For EDC, authors state participants were representative of T1D population of Allegheny County, PA	Unclear	Information bias: low Selection bias: low
Shalitin 2012[45] **JBI Score: 6**	Tertiary care university hospital-based study	NS	N/A (single-center patient medical records)	Highly specific definition based on medical records; likely low	Unclear; patients were treated at a specialized tertiary care center	Unclear, but authors state there was up to 7 yrs of follow-up data on patients after CSII initiation	Information bias: low Selection bias: low

Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; JBI = Joanne Briggs Institute; N/A = not applicable; NS = not stated; PA = Pennsylvania; RCT = randomized controlled trial; T1D = type 1 diabetes mellitus; yr = year.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9. In this manuscript, for the purposes of ease of discussion, a descriptive quality rating of "high" was given to studies with 8 or more Yes responses, and a descriptive quality rating of "low" was given to studies with 3 or fewer "Yes" responses. Studies with more than 3 and fewer than 8 "Yes" responses were described as "moderate" quality.

†The study authors cite this source: *N Engl J Med.* 1993 Sep 30;329(14):977-986; however, upon review, the source did not describe definition of DKA in the DCCT, nor did a high-level Internet search.

Table 2. Summary of Study Limitations for Studies Reporting Prevalence of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Beck 2012[35] **JBI Score: 7**	Clinic-based registry	Stratified data provided for patients with confirmed T1D†	Very good	Self-report, potential for misclassification	Patient treated by endocrinologists	All patients in registry during specific study time period	Information bias: yes (past events) Selection bias: possible
Butalia 2013[22] **Butalia 2014**[23] **JBI Score: 8**	Linked database analysis	NS	N/A (used linked database data)	Valid; based on hospitalization	Unclear	Patients in the Diabetes, Hypertension and Cholesterol Centre database (2 centers)	Information bias: low Selection bias: possible
Cengiz 2013[24] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-reported hospitalization)‡	Patients treated by endocrinologists	All patients meeting age and disease duration requirements during study time period	Information bias: yes (past events) Selection bias: possible
Laimer 2016[42] **JBI Score: 9**	Clinic-based registry	NS	N/A (used clinic-based patient data)	Standardized, likely low	Unclear	Unclear why this is such a small subset of the overall DPV database population	Information bias: low Selection bias: unclear
Miller 2015[38] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-report); only reported for prior 3 months	Patients all treated by endocrinologists§	All patients in registry during study period who had DKA data from a web-based questionnaire	Information bias: possible (past events) Selection bias: possible
Simmons 2013[39] **JBI Score: 7**	Clinic-based registry	Not explicitly described in this publication	Not stated in this publication	Likely (self-report)	Patients are all treated by endocrinologists, which may introduce some selection bias	Did not include patients with missing data on type of insulin administration or users of real-time CGM	Information bias: possible (past events) Selection bias: possible

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Sparud-Lundin 2008[43] **JBI Score: 3**	Clinic-based study	Not stated	86% of potential participants were included; 79% longitudinally followed	Relied on pH value, could be misclassified. 11.5% of the DKA values were missing at the latest time point	Patients all treated at 1 pediatric diabetes clinic and then had to be treated at 1 of 6 adult clinics	Unclear, assumed to be age-specific patient groups (not person-time)[‖]	Information bias: low Selection bias: possible
Trief 2014[31] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS; this analysis only includes patients with PHQ-8 data[‖]	Yes (self-reported hospitalization)[‡]; only reported for prior 3 months	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period who had PHQ-8 data	Information bias: possible (past events) Selection bias: possible
Weinstock 2013[13] **JBI Score: 8**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period	Information bias: possible (past events) Selection bias: possible
Wong 2014[40] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during specific study time period	Information bias: possible (past events) Selection bias: possible

Key: CGM = continuous glucose monitoring; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; JBI = Joanna Briggs Institute; N/A = not applicable; NS = not stated; PHQ-8 = Patient Health Questionnaire-8 response; T1D = type 1 diabetes mellitus.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9.

[†]Confirmation of T1D diagnosis was problematic for some adult-onset patients with incomplete clinical data; therefore, this group of patients may include some adults with T2D who were misdiagnosed with T1D.

[‡]The frequency of DKA occurrence reported by the clinics from medical record extraction was lower compared to patients' self-report of DKA events.

[§]The authors mention that "uninsured individuals are likely underrepresented in the cohort and pump use may be higher than it is in the overall population of type 1 diabetes in the US".

[‖]PHQ-8 is an 8-item questionnaire that was given at the 1-year data collection point to participants aged ≥18 years.

Appendix 1. Search Strategy Protocol

Submitted as supplementary file.

Appendix 2. Incidence and Prevalence of DKA

Submitted as supplementary file.

Appendix 3. DKA Risk Factors and Associations

Submitted as supplementary file.

Appendix 4. Quality Assessment of Included Studies (JBI Prevalence Studies Checklist)

Submitted as supplementary file.

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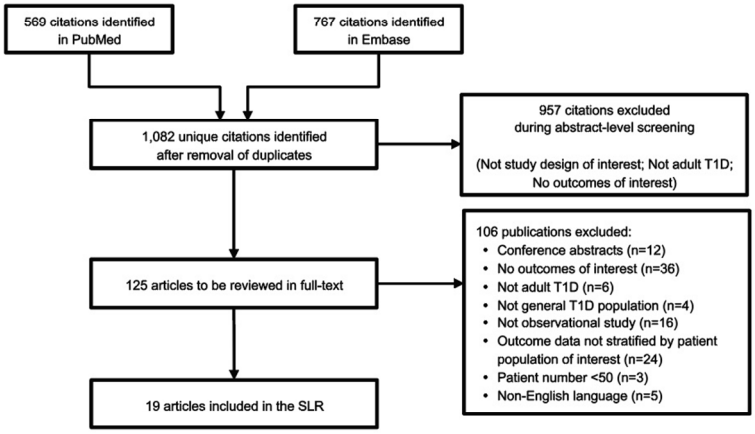

Literature Selection and Review Process

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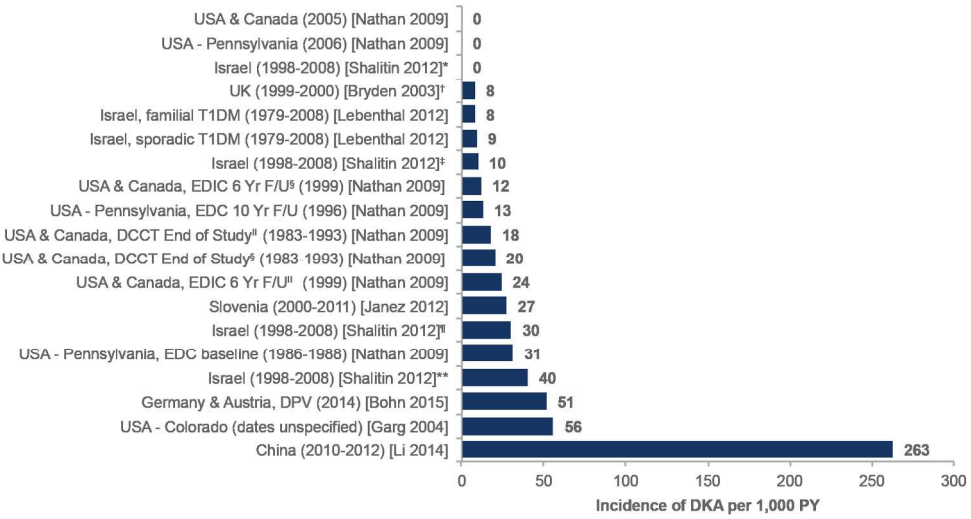

Incidence Rate per 1,000 PY of DKA in Adults With T1D (Reported in 8 Studies)

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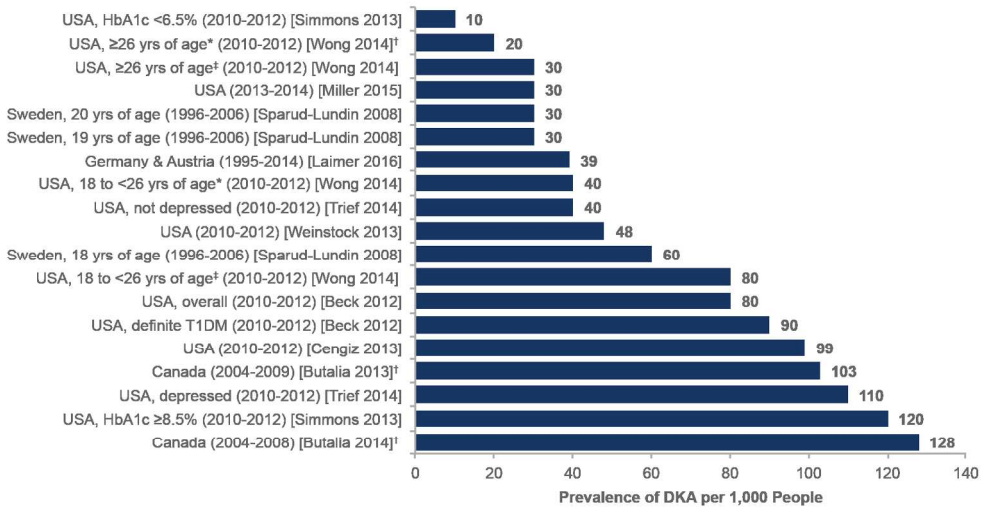

Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies) A) Overall

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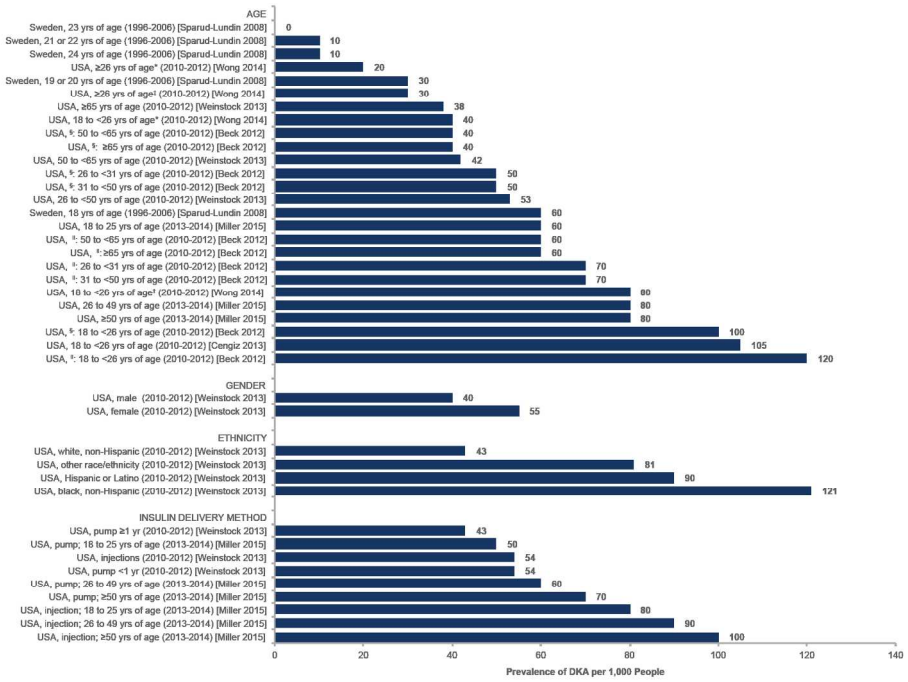

Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies) B) By Subgroups of Interest

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Systematic Literature Review of the Incidence and Prevalence of Diabetic Ketoacidosis among Adults with Type 1 Diabetes

Search Strategy, v2 (FINAL)

Prepared for:

Dr. Soulmaz Fazeli Farsani, Global Epidemiology
Boehringer Ingelheim GmbH

June 27, 2016

Xcenda AmerisourceBergen

AmerisourceBergen

TABLE OF CONTENTS

1.0 INTRODUCTION

Boehringer Ingelheim (BI) GmbH seeks to better understand the available published data describing the incidence and prevalence of diabetic ketoacidosis (DKA) in adults with type 1 diabetes mellitus (T1DM), including any relevant epidemiological data reported for stratified patient subgroups (such as by age, gender, geographic location, ethnicity, or typical method of insulin administration). To achieve this, Xcenda will perform a systematic literature review (SLR) which will follow the processes outlined within this study protocol.

The purpose of this protocol is to prospectively define the specific parameters by which the SLR of the incidence and prevalence of DKA in adults with T1DM will be conducted. Once agreed to by all parties, Xcenda will follow this protocol for all aspects of the review. Any changes made after agreement may impact the final research findings, associated project fees, and timeline. A change log of protocol amendments is located in Appendix A.

2.0 KEY RESEARCH QUESTIONS

This study will seek to answer the following key question and related query:

1. What is the overall incidence and prevalence of DKA in adult patients (≥ 18 years, including elderly patients) with T1DM?
    a. What is the incidence and prevalence of DKA in adult T1DM patients by subgroups (when reported in the manuscript and if possible to determine), including: age, gender, geographic location, ethnicity, type of insulin administration (insulin pumps versus injections)?

3.0 SEARCH STRATEGY

The overall approach to the search is outlined below. Additional features of the search strategy and search terms are further detailed in Section 5.0.

3.1 Data Sources

- MEDLINE (via PubMed)
- Embase

3.2 Search Filters and Limitations

3.2.1 Timeframe

- Studies published between January 1, 2000 and the date of the search will be included

3.2.2 Language and Countries

- Language: English only[1]
- Geography: no geographic limitations will be applied, but areas of greatest interest include North and South America, Europe, Japan, Taiwan, and Australia.

[1] Articles that appear relevant but are not published in English will be noted during screening and citations will be provided to BI for review.

3.2.3 Humans

- Only studies conducted in humans will be identified by the search.

3.2.4 Publication Status

- Published studies will be considered; conference abstracts will not be included in the review.

4.0 STUDY SELECTION CRITERIA

4.1 Population

- Adult (≥18 years) patients with T1DM
  - Elderly patients will be included
  - Studies of mixed populations (pediatric and adult, and/or type 1 and type 2 diabetes) will be included if stratified data are reported for adult T1DM patients. These publications will be categorized in a separate table.

4.2 Interventions/Comparators

The SLR will include all T1DM patients, regardless of treatment. Type of insulin and route of administration are of particular interest and will be captured when these data are available in the literature.

4.3 Outcomes

- Study endpoints (for overall patient population and relevant subgroups)
  - Incidence of DKA
  - Prevalence of DKA

4.4 Study Design

Included study designs:

- Population-based observational studies
- SLRs and meta-analyses[2]

Excluded study designs:

- Randomized controlled trials / clinical trials
- Pharmacokinetic and pharmacodynamic studies
- Non-randomized interventional studies
- Preclinical or animal studies
- Editorials, letters, and commentaries
- Case studies, reports, or case series

[2] Reference lists of SLRs will be hand-searched for any articles that may have been missed by the database search. If additional studies are identified (published from 2000 onwards), the data from those studies will be extracted separately. Data extraction for SLRs will only include a basic summary of the study design and overall results.

- Theses and dissertations
- Narrative literature reviews
- Small studies (n<50)
- Guidelines

5.0 SEARCH TERMS

Table 5-1 outlines the search terms to be considered as well as specific details on the search strategy.

Table 5-1. Search Strategy (with Sample Searches in MEDLINE and Embase)

Database	MEDLINE (via PubMed)	
Search Limitations or Filters Applied	Publication dates: 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	(((((((diabetes mellitus, type 1[MeSH Terms]) OR type 1 diabetes[Title/Abstract]) OR juvenile onset diabetes[Title/Abstract]) OR brittle diabetes[Title/Abstract]) OR insulin dependent diabetes[Title/Abstract]) OR iddm[Title/Abstract]) OR autoimmune diabetes[Title/Abstract]) OR sudden onset diabetes[Title/Abstract]	85,033
#2	(((diabetic ketoacidosis[MeSH Terms]) OR diabetic ketoacidosis) OR diabetic acidosis) OR diabetic ketosis	8,267
#3	((((adult[MeSH Terms]) OR adult) OR young adult) OR middle age) OR elderly	6,589,216
#4	#1 AND #2 AND #3	1,265
#5	review NOT (systematic OR (meta AND analys*))	2,372,581
#6	#4 NOT #5	1131
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**596**

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	'diabetes mellitus, type 1'/exp OR 'type 1 diabetes mellitus':ab,ti OR 'juvenile onset diabetes':ab,ti OR 'brittle diabetes':ab,ti OR 'insulin dependent diabetes':ab,ti OR iddm:ab,ti OR 'autoimmune diabetes':ab,ti OR 'sudden onset diabetes':ab,ti	106,633

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#2	'diabetic ketoacidosis'/exp OR 'diabetic acidosis'/exp OR 'diabetic ketosis'/exp	9,093
#3	'adult'/exp OR 'young adult'/exp OR 'middle age'/exp OR 'elderly'/exp	6,066,920
#4	#1 AND #2 AND #3	1,078
#5	review NOT (systematic OR (meta AND analys*))	3,002,962
#6	#4 NOT #5	950
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**766**

6.0 DATA EXTRACTION

Data extraction will be conducted in MS Excel and converted into MS Word tables for the final report. The elements for data extraction are outlined in Table 6-1.

Table 6-1. Example Data Extraction Templates

Author, year	Country	Type of study	Study period	Definition of DKA	Guidelines used for defining DKA	T1DM cases were identified based on?	Study participants				
							Mean, median, and range of age (as available)	Male%	Inclusion/ exclusion criteria	Sample size	Ethnicity

Author, year	Type of insulin	Insulin pump (Y/N)	Follow up years	N of new cases of DKA	Denominator for calculating rates of DKA	INC of DKA per 1000 PY	PREV of DKA per 1000 people	Conclusions	Notes/Comments/study limitations

APPENDIX A: PROTOCOL CHANGE LOG

Date	Protocol Section	Amendment	Status
Date of change	*Section X*	*Description of change*	*Completed Y/N*
8 July 2016	Section 6.0 Data Extraction	Additional DKA-related data (specifically potential risk factors associated with DKA) as reported in the included studies will be captured during data extraction.	Y

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
US and Canada								
Beck 2012[35]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	25,833*	NR	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 80† Definite T1D: 90
Butalia 2013[22]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, and census in Canada	1,994	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	127.9‡
Butalia 2014[23]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, census, and database of postal codes in Canada	1,467	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	102.9‡
Cengiz 2013[24]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	13,487 DKA subset, n=13,005 Aged 18 to <26 yrs subset, n=3,624	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 99
Garg 2004[37]	Retrospective analysis from a single center	Electronic patient record system in US	515	NR	Patient medical records	Number of patients who had a DKA event over the study period	Cumulative incidence: 55.6‡	NR
Miller 2015[38]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	16,061* DKA subset, n=2,561	Participant-reported DKA diagnosed by a doctor that required treatment in a	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Overall: 30

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
				healthcare facility				
Nathan 2009[36]	Observational, longitudinal cohort study	EDIC study (extension of DCCT in Canada and US) EDC study in US	***Conventional treatment*** DCCT, n=730 EDIC, n=606 ***Intensive treatment*** DCCT, n=711 EDIC, n=620 ***EDC*** Baseline, n=161; Year 10, n=105; Year 18, n=88	NR	NR	Incidence rate per 1,000 PY	***Conventional treatment*** DCCT: 18 EDIC Year 6: 24 EDIC Year 12: 0 ***Intensive treatment*** DCCT: 20 EDIC Year 6: 12 EDIC Year 12: 0 ***EDC*** Baseline: 31 Year 10: 13 Year 18: 9	NR
Simmons 2013[39]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	1,894	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Excellent HbA1c control (<6.5%): 10 Fair/poor HbA1c control (≥8.5%): 120
Trief 2014[31]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	6,172	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Depressed: 110 Non-depressed: 40
Weinstock 2013[13]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	7,012 DKA subset, n=6,796	Patient-reported overnight hospitalization for DKA Clinic-documented hyperglycemia and symptoms such as polyuria, polydipsia, nausea, or vomiting; serum ketones or large/moderate urine ketones; arterial blood pH <7.30, or venous pH	Patient self-report via questionnaire (these data were used for all primary analyses)	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 48

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
				<7.30, or serum bicarbonate <15 mmol/L; and treatment provided in a healthcare facility				
Wong 2014[40]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	17,317*	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	***18 to <26 yrs*** CGM user: 80 CGM non-user: 40 ***≥26 yrs*** CGM user: 30 CGM non-user: 20
Europe								
Bohn 2015[29]	Cross-sectional analysis of prospective, clinic-based patient registry	DPV prospective database of T1D patients in Germany and Austria	18,028	pH value <7.3 or hospital admission due to DKA	Patient medical records	DKA events per 100 PY	51.3	NR
Bryden 2003[30]	Single-center longitudinal cohort study	Case register of a young adult diabetic clinic in United Kingdom	113	Hospital admissions for DKA	Patient medical records	Number of patients with ≥2 admissions for DKA over 1,261 PY of follow-up	7.9‡	NR
Janez 2012[41]	Prospective, single-center, clinic-based patient registry	Registry of adult T1D patients treated with CSII in Slovenia	184	NR	Patient medical records	Number of patients with a DKA episode over the study period	Cumulative incidence: 27.2	NR
Laimer 2016[42]	Cross-sectional analysis of prospective, clinic-based patient registry	DPV prospective database of T1D patients in Germany and Austria	5,545	Hospital admission due to ketoacidosis with hyperglycemia >11 mmol/L and pH <7.3	Patient medical records	Percentage of patients with a DKA event	NR	39
Sparud-Lundin 2008[43]	Single-center, clinic-based longitudinal cohort study	Diabetes outpatient medical/nursing records from	104	Blood pH <7.30	Patient medical records	Number and percentage of patients with a DKA event for each year (from 18–24 yrs)	NR	Aged 18: 60 Aged 19: 30 Aged 20: 30 Aged 21: 10

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
		age 18–24 yrs in Sweden						Aged 22: 10 Aged 23: 0 Aged 24: 10
Other Regions								
Lebenthal 2012[25]	Retrospective analysis	Medical records from a single center in Israel	452*	Blood pH <7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	DKA events per 100 PY	Familial T1D: 8 Sporadic T1D: 9	NR
Li 2014[44]	Cross-sectional, multicenter, clinic-based study	Patient medical records from 16 tertiary hospitals in China	611*	Hyperglycemia (blood plasma glucose >13.9 mmol/L), blood bicarbonate <15 mmol/L and/or pH <7.30 (arterial), and elevated level of ketones in the urine or blood	Patient medical records; diagnosis based on criteria of the Chinese Diabetes Society, the American Diabetes Association , Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology	DKA events per 100 PY	263	NR
Shalitin 2012[45]	Retrospective analysis of patient medical records from a single center	Medical records from a single center in Israel ***Group 1:*** CSII initiated within 1 year of diagnosis ***Group 2:*** CSII initiated at least 1 year post-diagnosis	488*	Blood pH < 7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	Average number of DKA events per patient per year	***Group 1*** >19 yrs at last visit: 10 >19 yrs at CSII initiation: 0 ***Group 2*** >19 yrs at last visit: 40 >19 yrs at CSII initiation: 30	NR

Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; DPV = Diabetes-Patienten-Verlaufsdokumentation; ICD-10-CA = International Classification of Diseases, 10th Revision with Canadian Enhancements; NR = not reported; PY = person-years; SLR = systematic literature review; T1D = type 1 diabetes mellitus; US = United States; yrs = years.

* Overall study population; includes pediatric T1D patients (outcome data not included for pediatric patients).

† The overall patient population includes both definite T1D cases (patients meeting all diagnostic criteria) and probable T1D cases (patients meeting only some of the diagnostic criteria); the results for the definite T1D population were reported separately.

‡ Shaded (gray) cells represent outcome data that were calculated by the authors of this SLR based on the information available in the publication, rather than data directly reported by the study authors. Cumulative incidence was calculated/defined as number of cases out of total study population.

Reference	Methods	Measures of DKA Association/Risk	Comments
Bohn 2015[29]	Multiple Poisson regression models adjusted for age, sex, and diabetes duration, with treatment center as a random factor provided adjusted estimates of the incidence of DKA events per 100 PY: mean (standard error)	Adjusted estimate of DKA events per 100 PY: mean (standard error) Inactive patients (n=11,357): 6.48 (0.03) Patients who were physically active 1–2 times per week (n=3459): 3.99 (0.03) Patients who were physically active >2 times per week (n=3212): 2.40 (0.03)	**A significant inverse association was found between rates of DKA and level of physical activity** for the overall study population and for all subgroups (all *P*<0.0001)
Bryden 2003[30]	Multiple and logistic regression analyses with dependent variables: psychiatric referral, recurrent DKA admissions over the study period, any serious diabetic complication, HbA1c, and psychiatric symptoms at follow-up Independent variables entered into the model at baseline were sex, psychiatric symptoms, HbA1c, duration of diabetes, BMI, number of daily injections, and marital status Sex and baseline psychiatric symptoms were forced into the model, but other covariates that were not statistically significant at the 10% level were excluded from final models	Presence vs absence of psychiatric symptoms at baseline: **OR: 9.1; 95% CI: 2.9 to 28.6; *P*<0.0001** for recurrent admissions for DKA	**Patients with recurrent admissions for DKA over the study period were significantly more likely to have developed diabetic complications at follow-up than patients without recurrent DKA admissions**, and in multiple regression analyses, recurrent admissions for DKA over the study period predicted psychiatric symptoms at follow-up
Butalia 2013[22]	Logistic regression was used to calculate simple bivariate ORs for the associations between the DKA outcome and individual predictor variables. This was then followed by multivariable logistic regression modelling, for which backward elimination was performed to construct a parsimonious prediction model Variable elimination was carried out in thematic groups: the healthcare system, socioeconomic status, comorbidities, diabetes complications, indicators of complications, BMI, age, and sex	In univariate analyses, DKA hospitalization was associated with: Younger age **OR: 0.98 per year; 95% CI: 0.97 to 0.99** Lower BMI **OR: 0.94; 95% CI: 0.92 to 0.97** Shorter duration of T1D **OR: 0.97 per year; 95% CI: 0.96 to 0.98** Use of statin medications lowered the risk of DKA hospitalization **OR: 0.60; 95% CI: 0.42 to 0.86** Several comorbidities and complications were associated with increased risk of DKA hospitalization: Gastroparesis **OR: 3.85; 95% CI: 1.90 to 7.89** Psychiatric diagnosis **OR: 1.90; 95% CI: 1.21 to 2.97** Increased eGFR **OR: 1.12 per 10 mL/min 1.73 m^2; 95% CI: 1.06 to 1.17** Higher HbA1c **OR: 1.29 per 1% increase; 95% CI: 1.20 to 1.39** was associated with DKA hospitalization Higher quartiles of income compared with the lowest quartile (quartile 2, **OR: 0.66; 95% CI: 0.46 to 0.96**; quartile 3, **OR: 0.66; 95% CI: 0.45 to 0.95**; quartile 4: **OR 0.8; 95% CI: 0.68 to 0.96**) and more formal education (**OR: 0.42; 95% CI: 0.18 to 0.97**) lowered the odds of DKA hospitalization In multivariable logistic regression, longer duration of T1D was associated with lower odds of DKA hospitalization (**OR: 0.96 per year; 95% CI: 0.95 to 0.98**). Other factors significantly associated with DKA hospitalization included gastroparesis (**OR: 4.13; 95% CI: 1.82 to 9.35**), psychiatric diagnosis (**OR: 1.98; 95% CI: 1.22 to 3.19**), and higher HbA1c (**OR: 1.25; 95% CI: 1.16 to 1.35**)	

Reference	Methods	Measures of DKA Association/Risk	Comments
Butalia 2014[23]	Multivariate logistic regression analyses were used to assess the association between driving distance from patient residence to outpatient diabetes care sites and the DKA outcome Unadjusted and adjusted models for clinical and sociodemographic factors also were constructed for DKA hospitalization. Clinical factors included BMI, duration of diabetes, specialist care, comorbidities and complications, HbA1c, and eGFR. Other variables included sex, age, median family income, and neighborhood education level (proportion with university degree/diploma/certificate)	In multivariate analyses, driving distance from home to diabetes center 1 (adjusted OR: 1.02 per 1 km; 95% CI: 0.96 to 1.07) to diabetes center 2 (adjusted OR: 1.01; 95% CI: 0.99 to 1.04) or to closest general practitioner (adjusted OR: 0.9; 95% CI: 0.63 to 1.25) was not associated with DKA hospitalization	Patients with DKA hospitalization were younger, had shorter duration of T1D, and had higher HbA1c than patients without DKA hospitalization
Cengiz 2013[*24]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01. Interactions among age, diabetes duration, sex, and HbA1c were evaluated, and no interaction term was significant at the level of 0.01	Detailed data on OR for adjusted and unadjusted models and numerous patient stratifications are available in Table 3 and Supplemental Table 2 of the publication	After adjusting for age, a higher **frequency of DKA was significantly associated with female sex, non-white race, lower income, no private insurance, higher HbA1c, and MDI insulin method (vs pump); (all *P*<0.001).** In a multivariate analysis**, female sex, higher HbA1c, non-white race, lower income, and lack of private insurance continued to be significantly associated with a higher frequency of DKA**. Results were similar for each age group.
Laimer 2016[42]	Linear regression analysis adjusted for age, sex, duration of diabetes, and basal insulin rate per kg body weight was used to analyze the association between basal rate variability and DKA	In male adult T1D patients, a **higher variability index of basal insulin rates was associated with higher frequency of DKA (r=0.04; *P*=0.029)** Logistic regression analysis (adjusted for age, sex, duration of disease, and total basal insulin) **confirmed significant positive correlations of the variability index of basal insulin rates with DKA (β=0.012; *P*=0.017) and between basal insulin rates (basal rate/kg/24h) and DKA (β=1.743; *P*<0.001),** but not with age (β=0.008; *P*=0.159), duration of disease (β=0.001, *P*=0.884), or sex (β=0.205, *P*=0.154) and DKA	
Lebenthal 2012[25]	Multiple logistic regression by stepwise backward methods was applied to determine variables significantly associated with acute complications	Overall rates of DKA events were significantly higher in familial than in sporadic cases (2.8 vs 1.9 events per 100 PY) **IRR=1.5; 95% CI: 1.03 to 2.22; *P*=0.03** Note that this association was not significant for patients aged >19 years (IRR=0.92 [95% CI: 0.36 to 2.32], *P*=0.87)	A higher mean HbA1c level was a predictor for DKA events in both the familial and the sporadic groups, whereas age at diagnosis of T1D and sex did not predict DKA events in either group
Li 2014[44]	A Poisson regression model was used to determine risk factors for secondary DKA. Separate backwards stepwise logistic regression analyses were used to identify risk factors for the recurrence of secondary DKA	Detailed data on relative risk are available in Figure 1 of the publication and results of logistic regression analyses for secondary DKA recurrence are reported in Table 2 For the overall population, the following parameters were significant risk factors for secondary DKA:	There were no significant differences in DKA incidence between patients treated with insulin glargine and patients treated with NPH insulin Regarding recurrences, 34.4% of secondary DKA episodes represented

Reference	Methods	Measures of DKA Association/Risk	Comments
		Female sex (**RR=2.12; 95% CI: 1.50 to 3.04**) Medical reimbursement rates <50% (**RR=1.84; 95% CI: 1.33 to 2.60**) Uncontrolled diet ("never controlled" vs "usually controlled") (**RR=1.76; 95% CI: 1.18 to 2.57**) Smoking (**RR=2.18; 95% CI: 1.30 to 3.59**) Poor glycemic control (HbA1c per1.0% increase, **RR=1.15; 95% CI: 1.10 to 1.21**) An overweight/obese BMI (vs normal) significantly reduced the risk of secondary DKA (**RR=0.57; 95% CI: 0.31 to 0.96**) In logistic regression models, recurrence of secondary DKA was associated significantly with: Female sex (**RR=10.56; 95% CI: 1.97 to 56.72; *P*=0.01**) Smoking (**RR=6.99; 95% CI: 1.02 to 48.00; *P*=0.05**) Poor β cell function (stimulated C-peptide/100 pmol/L decrease (**RR=4.22; 95% CI: 1.20 to 6.97; *P*=0.01**) Poor glycemic control (HbA1c per1.0% increase, (**RR=1.16; 95% CI: 1.00 to 1.34; *P*=0.05**)	recurrent events (≥2 episodes) in 3.8% of the patients
Miller 2015[38]	No statistical modelling analyses reported; qualitative summary data only	NR	The frequency of DKA tended to be higher among participants with higher HbA1c levels and slightly lower among participants using an insulin pump
Shalitin 2012[45]	No statistical modelling analyses reported; summary data only based on Pearson's chi-square test or Fisher's exact test	NR	The rates of DKA episodes were not significantly different between the 2 groups (patients who initiated CSII within 1 year of diagnosis or patients who initiated CSII at least 1 year after diagnosis), either in total or on subanalysis by age groups, pubertal stages, diabetes duration, or CSII treatment duration
Trief 2014[31]	Diabetes-management outcomes (including DKA) in those with and without depression were compared using linear regression for continuous variables and logistic regression models for categorical variables	Compared with non-depressed participants, depressed participants had more frequent DKA events in the past 3 months (**11% vs 4%; *P*<0.001** for all 3 definitions of depression) Compared with lower-scoring participants, participants with higher depression scores were more likely to experience more frequent DKA (***P*<0.001)** NR	

Reference	Methods	Measures of DKA Association/Risk	Comments
Weinstock 2013[13]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01	Detailed data on OR and 95% CI from logistic regression models evaluating the association between baseline demographic and clinical characteristics and the occurrence of a patient-reported or clinic-reported DKA event are described for numerous patient subgroup stratifications in Table 2 and Supplemental Table 3 of the publication	Frequency of DKA was lower with increasing age. However, the age effect was largely explained by HbA1c level, which was strongly associated with the occurrence of a DKA event. Frequency of DKA was not associated with diabetes duration In addition to HbA1c level, **a higher frequency of DKA was associated with lower socioeconomic status based on education level, income, and insurance status (*P*<0.001 for each in multivariate model) and female sex (*P*=0.008)**. In univariate models, non-Hispanic black and Hispanic participants had higher frequencies of DKA than non-Hispanic whites, and current smokers had higher frequency of DKA than nonsmokers, but after adjusting for socioeconomic status, neither factor was significant in the multivariate model. Frequency of DKA was not significantly different between pump and injection users
Wong 2014[40]	Logistic regression modelling adjusted for sex, race/ethnicity, education level, annual household income, health insurance status, diabetes duration, and insulin delivery method (pump/ injection)	CGM UYser vs CGM non-user: <u>18 to <26 yrs:</u> Unadjusted OR: 0.5; 95% CI: 0.2 to 1.0; *P*=0.06 Adjusted OR: 0.6; 95% CI: 0.2 to 1.8; *P*=0.33 <u>≥26 yrs:</u> Unadjusted OR: 0.7; 95% CI: 0.4 to 1.1; *P*=0.09 Adjusted OR: 1.4; 95% CI: 0.8 to 2.3; *P*=0.23	CGM use was not significantly associated with rates of DKA for these age groups in logistic regression models

Key: BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin A1c; IRR = incidence rate ratio; NPH = neutral protamine Hagedorn; NR = not reported; OR = odds ratio; PY = person-years; RR = relative risk; T1D = type 1 diabetes mellitus.

Bold text highlights associations that were found to be statistically significant in each study.

* Associations were calculated based on the full patient population (which included pediatric patients); however, analyses were adjusted for age.

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview **N=21 studies**	**12 (57%) Yes** **7 (33%) Unclear** **2 (10%) No**	**17 (81%) Yes** **3 (14%) Unclear** **1 (5%) No**	**15 (71%) Yes** **5 (24%) Unclear** **1 (5%) No**	**18 (86%) Yes** **0 (0%) Unclear** **3 (14%) No**	**15 (71%) Yes** **5 (24%) Unclear** **1 (5%) No**	**9 (43%) Yes** **12 (57%) Unclear** **0 (0%) No**	**11 (52%) Yes** **9 (43%) Unclear** **1 (5%) No**	**18 (86%) Yes** **3 (14%) Unclear** **0 (%) No**	**16 (76%) Yes** **4 (19%) Unclear** **1 (5%) No**
Beck 2012[35]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Bohn 2015[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bryden 2003[30]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2013[22]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2014[23]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cengiz 2013[24]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Garg 2004[37]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Janez 2012[41]	No	No	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear
Laimer 2016[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lebenthal 2012[25]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear
Li 2014[44]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Miller 2015[38]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Nathan 2009[36]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Shalitin 2012[45]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Simmons 2013[39]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview N=21 studies	**12 (57%) Yes 7 (33%) Unclear 2 (10%) No**	**17 (81%) Yes 3 (14%) Unclear 1 (5%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**18 (86%) Yes 0 (0%) Unclear 3 (14%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**9 (43%) Yes 12 (57%) Unclear 0 (0%) No**	**11 (52%) Yes 9 (43%) Unclear 1 (5%) No**	**18 (86%) Yes 3 (14%) Unclear 0 (%) No**	**16 (76%) Yes 4 (19%) Unclear 1 (5%) No**
Sparud-Lundin 2008[43]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Trief 2014[31]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Weinstock 2013[13]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Wong 2014[40]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Key: JBI = Joanna Briggs Institute.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-14; Figs 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 1 & 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

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Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review

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Incidence and prevalence of diabetic ketoacidosis (DKA) among adults with type 1 diabetes mellitus (T1D): a systematic literature review

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ABSTRACT

OBJECTIVES

To summarize incidence and prevalence of diabetic ketoacidosis (DKA) in adults with type 1 diabetes (T1D) for the overall patient population and different subgroups (age, sex, geographical region, ethnicity, and type of insulin administration).

DESIGN

Systematic literature review (SLR)

DATA SOURCES

MEDLINE (via PubMed) and Embase (1 January 2000 to 23 June 2016).

STUDY SELECTION

Peer-reviewed observational studies with reported data on the incidence or prevalence of DKA in T1D adults were included. A single reviewer completed the study screening and selection process and a second reviewer performed an additional screening of approximately 20% of the publications; two reviewers independently conducted the quality assessment; the results were narratively synthesized.

RESULTS

Out of 1,082 articles, 19 met the inclusion and exclusion criteria, with two additional studies identified that did not specify the patient age range and are therefore not included in the SLR. Overall, eight studies reported incidence with a range of 0–56 per 1,000 person-years (PYs), with one outlying study reporting an incidence of 263 per 1,000 PYs. Eleven studies reporting prevalence with a range of 0–128 per 1,000 people. Prevalence of DKA decreased with increasing age. 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..

CONCLUSIONS

To our knowledge, this is the first SLR on the epidemiology of DKA in T1D adults. Despite an increasing prevalence of T1D in recent years, DKA in adults has been poorly characterized. In an era when the benefit-risk profiles of new antidiabetic therapies are being evaluated, including the potential risk of DKA, there is a clear need to better elucidate the expected rate of DKA among T1D adults.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

- To our knowledge, this is the first literature review to systematically assess and summarize the incidence rate and prevalence of DKA in adults with T1D.
- Both young adults and the elderly were included in this SLR, so the results may be applicable across a wide spectrum of adult T1D patients.
- The quality of included studies was assessed using a standardized tool (the JBI prevalence studies quality assessment tool).
- This review, like any SLR, is subject to publication bias, as an SLR inherently relies upon data available in the published literature.
- Studies not published in English were excluded from the SLR, as were studies of fewer than 50 patients.

KEY WORDS: diabetic ketoacidosis; type 1 diabetes mellitus; systematic literature review; incidence; prevalence; epidemiology;

Introduction

Diabetes is a disease characterized by high blood glucose resulting from abnormal insulin production, function, or both.[1] Type 1 diabetes mellitus (T1D) is an autoimmune disease caused by the immune-mediated destruction of pancreatic beta cells.[1] This destruction is modulated by the body's immune system and leads to a limitation in, or complete cessation of, the production and secretion of insulin, which results in the need for external insulin delivery for survival.[1] T1D typically follows an acute clinical course, with patients presenting with polyuria, polydipsia, and weight loss.[2] According to the International Diabetes Federation (IDF), approximately 542,000 children 0−14 years of age have T1D, with 86,000 new cases diagnosed worldwide each year.[3] While there are geographical differences, the overall annual increase in the incidence of T1D is estimated at approximately 3−4%.[3, 4] Diagnosis of T1D typically occurs in childhood; in the United States (US), the peak (mean) age at diagnosis is approximately 14 years.

Information regarding the epidemiology of T1D specifically in adults is scarce; many epidemiological studies of adult patients categorize those with blood glucose levels above a certain threshold as simply diabetic, without providing more detailed data on the relative proportions of patients with T1D versus type 2 diabetes mellitus (T2D).[3] Approximately 5% of adult-diagnosed cases of diabetes are diagnosed as T1D,[1] although an Italian study has shown rates of T1D as high as 50% of incident cases of diabetes among normal-weight adults (aged 30−54 years).[5] 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 US1.[6-9] A recent systematic literature review (SLR) reported the incidence of T1D to be 1.5 times higher in males than in females less than 40 years of age.[6]

Diabetic ketoacidosis (DKA) is a major acute metabolic complication of T1D that is typically marked by acidosis, ketosis, and usually hyperglycemia.[10-12] The symptoms of uncontrolled

diabetes that may lead to development of DKA are typically of short duration and include polyuria, polydipsia, polyphagia, weight loss, vomiting, abdominal pain, and fatigue.[10-12] Diabetic ketoacidosis is diagnosed in different ways, but typically the following three factors are present: elevated plasma glucose (>250 mg/dL), ketones in serum or urine, and acidosis (serum bicarbonate <18 mEq/L and/or pH <7.30).[10] Management of DKA includes fluid and electrolyte therapy, insulin therapy, treatment of any identified triggering causes (eg, continuous subcutaneous insulin infusion (CSII) pump failure, sepsis, pneumonia, acute pancreatitis, cerebrovascular accident, myocardial infarction, stroke, trauma, medications that affect carbohydrate metabolism), and monitoring of therapy and resultant complications.[10, 12, 13] Excessively rapid fluid resuscitation should be avoided to prevent cerebral edema, a rare but debilitating and potentially fatal complication of DKA.[10] While inpatient mortality rates for DKA are generally very low (<1% in Scotland [14] and in the US [15]), rates vary substantially based on healthcare setting; a recent analysis conducted in India reported that up to 30% of hospitalized DKA cases result in inpatient death.[13] Among all T1D-related deaths for patients aged less than 30 years, 54%–76% can be attributed to DKA.[16-19] Risk factors associated with a higher frequency of DKA may include younger age at time of DKA hospitalization,[20, 21] higher mean glycosylated hemoglobin A1c (HbA1c),[11, 20-23] infection,[24] CSII pump failure,[25, 26] lower socioeconomic status/household income,[11, 20, 22] lower physical activity level,[27] and psychiatric symptoms/depression.[20, 28, 29] The prevalence of DKA at initial disease presentation in pediatric T1D patients is well documented [30, 31]; however, information on the prevalence or incidence in adults is limited. One study using the T1D Exchange Clinic Registry in the US found that 4.8% of participants reported one or more DKA events (requiring self-reported overnight hospitalization) in the previous 12 months.[11] The objectives of this SLR were to summarize the available epidemiological data (incidence rate and prevalence) for DKA in adult patients (aged ≥18 years) with T1D from population-based and other observational studies and to evaluate trends in the evidence for the overall patient population and specific subgroups (age, sex,

geography, ethnicity, and type of insulin administration such as CSII or multiple daily injections [MDIs]).

Methods

Search strategy and selection process

This systematic review was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.[32] The Study protocol (including search strategy and search terms) was developed and accepted by all authors prior to commencement of the search and can be found in Appendix 1. MEDLINE (via PubMed) and Embase databases were searched for articles published between January 1, 2000 and June 23, 2016 (date of search execution) by a single review author (EW). The searches were filtered for human studies, but no language restrictions or geographic limitations were applied to the search strategy. Note that only studies published in English were included. Relevant studies published in other languages were noted during screening and a list of these citations reviewed for consideration; it is of note that fewer than 10 non-English studies which had English abstracts available for review were identified and none were deemed relevant for inclusion based on the abstracts. Included studies were peer-reviewed, and ongoing studies without peer-reviewed publication (eg conference abstracts) were excluded. The search results were combined in a referencing software database, and duplicate records were removed.

Upon second-pass review, a single review author (EW or BAM) applied the following criteria. The targeted population was males and females aged at least 18 years with T1D. When sufficient data were available in the publications to permit determination of the patients' age range (for example, mean age and standard deviation [SD] or standard error), the relevant calculations were performed to determine eligibility for inclusion (for example, mean age ± three SD as an estimate of the range of study patients' age). If the mean age was reported and the

calculated age for minus three SDs was <18 years, the study was excluded, unless the study population was explicitly described as adults aged ≥18 years. Studies of mixed populations (pediatric and adult patients and/or T1D and T2D) were included only if stratified data were reported for adult T1D patients. This review was not restricted by specific interventions or comparators and included all T1D patients, regardless of treatment. 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. Type of insulin and method of administration were of interest and were captured when these data were available. Peer-reviewed population-based observational studies, SLRs, and meta-analyses of human studies were included. This SLR was originally intended to include only population-based studies but was expanded to include other observational study designs such as clinic-based and (potentially unrepresentative) registry studies since there was limited population-based studies in the peer-reviewed literature. Because the aim of the review was to assess real-world epidemiology reported in the peer-reviewed literature describing studies of humans, randomized controlled trials/clinical trials and interventional studies were excluded, as were preclinical or animal studies, editorials, letters, commentaries, case studies, reports or case series, theses and dissertations, narrative literature reviews, small studies (sample size of fewer than 50 patients), guidelines, and unpublished studies (eg, conference abstracts).

Data extraction and analysis

Data extraction was conducted by a single review author (EW or BAM) using a Microsoft® Excel file with standardized definitions for each data element that was extracted from each study (see Appendix 1). Data of interest were incidence rate of DKA (number of new DKA events out of accumulated patient time under study, in person-years [PYs]) and prevalence of DKA (number of DKA events among the total number of patients at risk). Data on risk factors and clinical parameters associated with DKA events were also extracted when reported in the included

publications. When sufficient data were available in the published literature to allow computation of these outcomes if not specifically reported by the authors (for example, the number or proportion of patients who experienced a DKA event over a defined time period), the appropriate calculations were performed and are noted as such. For two publications, cumulative incidence was calculated (number of new DKA events out of total patients at risk) because data on incidence rates were not directly reported in the publications. Results from data extraction, including incidence rate, prevalence, and risk factors for DKA, can be found in Appendices 2 and 3.

The quality of included studies was assessed by a trained epidemiologist (BAM), with consideration of the study design, disease ascertainment, response rate (if applicable), definition of DKA, representativeness of the study population, and major potential biases. A table describing these factors for each included study can be found in this report (Table 1). Additionally, a standardized quality assessment tool, the Joanna Briggs Institute (JBI) Critical Appraisal Tools "Checklist for Prevalence Studies" (available at http://joannabriggs.org/research/critical-appraisal-tools.html), was selected as an appropriate tool for assessment of the included study designs. Quality assessment of each included study using the JBI Checklist for Prevalence Studies was undertaken independently by two reviewers (EW and BAM), with any discrepancies resolved by a third reviewer (Xcenda employee, member of evidence synthesis team). The results of the quality assessment using the JBI tool can be found in Appendix 4.

Patient involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. No patients were asked to advise on

interpretation or reporting of results. There are no plans to disseminate the results of the research to patient communities.

Results

Figure 1 summarizes the literature review process, including the number of records identified, the screening and eligibility results, and the final list of included references. Out of 1,082 articles identified through the initial search, 19 peer-reviewed observational study publications met the inclusion and exclusion criteria; no SLRs or meta-analyses were identified that met the inclusion and exclusion criteria. There were 11 publications in North America (US and Canada),[11, 20-22, 29, 33-38] five publications in Europe,[27, 28, 39-41] and two publications in Israel and one publication in China.[23, 42, 43] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[23, 27, 28, 34, 35, 39, 42, 43] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[11, 20-22, 29, 33, 36-38, 40, 41] The lowest incidence rates were reported in Israel and North America (both 0 events per 1,000 PYs)[34, 43] and the highest in China (263 events per 1,000 PYs)[42] (Figure 2). The lowest prevalence was reported in Sweden (0 per 1,000 people)[41] and the highest in Canada (127.9 per 1,000 people)[21] (Figure 3a).

In terms of baseline characteristics, patient selection, and descriptions of outcomes, there were some broad similarities across studies included in this review. In most studies, specific definitions or diagnostic criteria for T1D were not described, and some studies did not fully report patient baseline demographic information such as patient ethnicity or insulin delivery method. Standardized measurements of DKA events were not frequently utilized, as many studies (seven of 19) relied on patient self-report of DKA episodes or hospitalization records (four of 19). Three publications[11, 22, 29] using data from the T1D Exchange Clinic registry directly compared DKA data as identified by patient self-reported and clinic-documented events and found that, while the frequency of participant-reported DKA events was higher than clinic-

reported events based on medical records, results from logistic regression models designed to assess potential associations with DKA episodes were similar for both sets of data.[11] Few exclusion criteria were applied to the patient populations, most commonly pregnancy and lack of available data. The age range of patient cohorts varied across studies, with some investigations (two of 19) restricted to young adults only (approximately 18–26 years of age), four studies focused on adults aged approximately 20–55 years, and most (12 studies) evaluating adults of all ages, including those aged over 65 years. Most (16 of 19) studies had approximately a 1:1 male-to-female ratio of patients. Ethnicity of the patient cohorts was only reported in eight studies; when reported, the vast majority of patients (>80%) were of white non-Hispanic ethnicity. In the publications providing data on insulin delivery method in unselected populations (11 of 19 studies), most (50%–60%) patients were treated with CSII. While the number of studies providing data on insulin delivery method was limited, there seemed to be an overall trend toward an increasing proportion of CSII users in more recent publications/study periods compared with older investigations.

Overall incidence and prevalence of DKA in North America

Eleven studies conducted in North America (US and Canada) reported incidence rate (2) or prevalence (9) for DKA events in adults with T1D (Appendix 2). Results from two long-term observational cohorts found that the incidence of DKA showed a general reduction over the duration of study follow-up, with an incidence rate of approximately 20 cases per 1,000 PYs at baseline to 0 events at the 12-year follow-up in one cohort and a decrease from approximately 30 cases per 1,000 PYs at baseline to <10 cases per 1,000 PYs at the 18-year follow-up in another cohort.[34] A US-based study from a single clinic in Colorado compared CSII pump users (42% of patients) to patients treated with MDIs (58% of patients) [35], over the study period of approximately 1 year, only patients treated with CSII experienced any DKA events. In this

investigation, the cumulative incidence of DKA was calculated to be 55.6 per 1,000 people for CSII users.

All of the publications describing prevalence of DKA in the US were based on data from the T1D Exchange Clinic Registry, although each investigation evaluated a slightly different patient population. All of these studies relied on patient self-report to determine occurrence of DKA events, and the recall period varied from three to 12 months. For most studies of the larger patient population from the registry, prevalence ranged from approximately 50 to 100 per 1,000 people.[11, 22, 33, 38] Slightly higher DKA prevalence than that reported in the US-based studies was observed in two studies from Canada, both of which linked data from the following databases to determine DKA prevalence: Diabetes, Hypertension, and Cholesterol Center in Calgary; Alberta Inpatient Discharge Abstract Database; Alberta Kidney Disease Network; and Statistics Canada 2006 Census Data.[20, 21] In these linked database studies, calculated prevalence was found to be 103 per 1,000 people [21] and 128 per 1,000 people.[20] These Canadian studies relied on linked data from hospital inpatient admissions rather than patient self-report.

Overall incidence and prevalence of DKA in Europe

In very broad terms, the incidence rates and prevalence reported for European studies (Appendix 2) were similar to those described in investigations conducted in North America; however, these trends should be considered with substantial caution given the very small number of European publications reporting each outcome. Only five publications described the epidemiology of DKA in adult patient populations in Europe; two reported on patients from the Diabetes-Patienten-Verlaufsdokumentation (DPV) database, which includes patients in Germany and Austria [27, 40]; and three evaluated small single-center patient cohorts.[28, 39, 41] In all cases, DKA events were ascertained based on patient medical records.

Incidence rates ranged from approximately 8 cases per 1,000 PYs (calculated rate based on hospital admissions for DKA) in a study of 113 young adults in Oxfordshire, England [28] to 51.3 cases per 1,000 PYs (reported rate based on pH <7.3 or hospital admission for DKA) for over 18,000 adult patients selected from the DPV database.[27] A Slovenian single-center study of patients treated with CSII [39] provided sufficient data to calculate cumulative incidence of 27.2 cases per 1,000, a lower value than that observed in a similar US-based study (55.6 per 1,000).[35] It should be noted that while the study period was unclear in the US investigation, based on publication date (2004 for the US study), it is likely that the Slovenian study (with a study period through 2011) included more recent data. This may have had an impact on DKA incidence given the technological improvements in insulin pumps and glucose monitoring over the duration of the Slovenian study (2000 through 2011, and patients had to have 3 or more years of complete data to be included in this study); indeed, the US study reported that the majority of DKA events recorded were due to pump malfunctions.

Prevalence of DKA was reported in two European studies.[40, 41] One single-center longitudinal study of 104 patients performed in Sweden [41] found a numerical (but not statistically significant) reduction in DKA cases with increasing year of age from 18 to 24 years (prevalence ranged from 0 to 60 cases per 1,000 people over this period and was calculated for each 1 year of age separately by the authors). A cross-sectional analysis of patients from the DPV database examining the association of variability in basal insulin rates with various outcomes reported the prevalence of DKA as 39 cases per 1,000 people,[40] also a slightly lower value than the prevalence data reported for US- or Canadian-based studies.

Overall incidence of DKA in other regions

Three studies conducted in other regions reported only incidence rate data (Appendix 2), with very low rates observed in two studies based on patient medical records from the same tertiary

care facility in Israel [23, 43] and very high rates described in a multicenter study conducted in tertiary care units in a single province in China.[42] The low incidence rates in the Israeli studies (ranging from 0 to 40 cases per 1,000 PY) may reflect some selection bias in the patient population treated at this single center.[23, 43] In the Chinese study,[42] the authors acknowledge that the incidence rate observed in their study (263 per 1,000 PY) is considerably higher than values cited in published reports from other countries. The investigators attribute this discrepancy, at least in part, to differences in national healthcare systems, which may limit access to routine healthcare for some T1D patients in China, as well as infrequent self-monitoring of blood glucose by patients and inappropriate treatment or errors in diabetes management. Although not explicitly described in the publication, it seems likely that this study reported the incidence rate of all DKA events during the study period, rather than only the first instance of DKA for each patient. The authors stated that in this study, more than a third (34.4%) of DKA events represented recurrent (two or more) episodes of DKA for 3.8% of patients, suggesting that a small population of very high-risk patients contributed substantially to the overall incidence rate.

DKA prevalence by age

Five publications from the US-based T1D Exchange Clinic Registry [11, 22, 33, 36, 38] reported prevalence of DKA among adults with T1D with outcome data stratified by age, as did 1 study conducted in Sweden and described previously in the "Overall incidence and prevalence of DKA in Europe" sub-section (Figure 3b).[41] In the US-based studies, four of the studies examined a broad sample of adult patients aged 18 to >90 years; one analysis [22] focused solely on young adults. Given the design of the registry, all five studies relied on patient self-report of past DKA events; three publications [11, 22, 33] examined the prior 12-month period and two [36, 38] queried patients about the previous three months. There was a general trend of decreasing DKA prevalence with increasing age observed across most studies providing age-stratified data.

Young adults (aged 18 years to 25 years) had the highest prevalence of DKA (100−120 cases per 1,000 in studies with 12-month recall and 40−80 cases per 1,000 in studies with three-month recall), while the elderly (aged ≥65 years) had the lower prevalence of DKA (38−60 cases per 1,000 in studies with 12-month recall). The only exception to this trend was a study in which prevalence of DKA was similar across all three adult age ranges (18−25 years, 26−49 years, and ≥50 years).[36] The DKA data in this particular investigation may have been affected by the study requirement that all patients had an annual follow-up visit at which HbA1c was measured and the shorter duration of recall for DKA events (three months). There was no information on incidence rate stratified by patient age reported in any studies identified by this SLR.

DKA prevalence by other patient subgroups of interest

Subgroup data for patients categorized according to clinical or demographic characteristics other than age, such as sex, ethnicity, insulin delivery method, glycemic control, and depression comorbidity were very limited, with data available from only 1 or 2 studies. As with patient stratification by age, only data on DKA prevalence were available for the other categorical variables reviewed. Based on these limited data, higher prevalence of DKA was observed for women versus men, non-white versus white ethnicities, depressed versus non-depressed patients, patients with fair/poor versus excellent glycemic control, and patients treated with insulin injections compared to those using CSII (Figure 3b).[11, 29, 36, 37]

In a single study designed to investigate cross-sectional associations between patient characteristics and DKA events,[11] female patients had a higher prevalence of DKA over the previous 12-month period than male patients (55 versus 40 cases per 1,000 people, respectively). This study also reported a prevalence of DKA in white non-Hispanic patients of 43 per 1,000, while all other ethnicities had considerably higher prevalence of DKA, ranging from 81 per 1,000 (other race/ethnicity) to 121 per 1,000 (black non-Hispanic) during the same study

period.[11] Higher prevalence of DKA was observed among depressed patients (110 per 1,000 for patients with at least one DKA event in the previous three months) than non-depressed patients (40 per 1,000 for patients with at least one DKA event in the previous three months).[29]

DKA was more prevalent in patients with fair or poor glycemic control, defined as HbA1c ≥8.5% (120 per 1,000 for patients with at least one DKA event in the previous 12 months).[37] In contrast, the lowest prevalence of DKA was reported for patients with excellent glycemic control, defined as HbA1c <6.5% (10 per 1,000 for patients with at least one DKA event in the prior 12 months).[37] Patients treated with CSII had lower prevalence of DKA than did patients using injectable insulin.[11, 36] This trend was seen across multiple age groups in one study.[36] However, duration of treatment with a CSII may affect prevalence of DKA, as data for patients who had recently (within the prior year) initiated pump therapy had similar rates of DKA to participants treated with insulin injections (both groups had 54 events per 1,000), and the lower DKA prevalence (43 events per 1,000) was observed only in patients who had been treated with a CSII for at least the previous year.[11] It should be noted that these numerical trends did not demonstrate a statistically significant difference between insulin delivery groups in this study.

DKA risk factors and associations

Over half of the included studies (13 publications) reported at least some data on risk factors or patient characteristics associated with DKA events [11, 20-23, 27-29, 36, 38, 40, 42, 43] (Appendix 3). Almost all of these investigations utilized multiple regression analyses to evaluate the associations between baseline parameters and risk of DKA, adjusted for potential confounding factors such as age, sex, body mass index (BMI), and duration of diabetes.[11, 20-23, 27-29, 36, 40, 42] Two of the studies that investigated risk factors associated with DKA only provided qualitative summaries of the associations.[36, 43]

Several studies identified patient characteristics that were significantly associated with increased risk of DKA.[11, 20, 22, 23, 36, 42] The most frequently reported parameters correlating with DKA events were higher HbA1c/poor glycemic control,[11, 20, 22, 23, 36, 42] lower socioeconomic status (based on income, formal education, and private insurance or some combination thereof),[11, 20, 22, 42] depression/psychiatric symptoms or diagnosis at baseline,[20, 28, 29] and female sex.[11, 22, 42] Regarding the patient subgroups of interest, some conflicting data were presented for the relationship between DKA events and ethnicity or insulin delivery method. In a population restricted to young adults only (aged 18 years to 25 years) from the T1D Exchange Clinic Registry, Cengiz and colleagues [22] found that both non-white race and use of MDIs (versus CSII) were significantly associated with an increased frequency of DKA events.[22] In contrast, in a study examining a broader adult population (also from the T1D Exchange Clinic Registry), while non-white race was significantly associated with greater frequency of DKA events in a univariate analysis, after adjusting for socioeconomic status, non-white race was no longer a significant predictor of DKA.[11] Similarly, this investigation [11] found no difference in rates of DKA based on insulin delivery method.

Quality assessment of included studies

Regarding the quality of the studies included in this SLR, while each study did have potential limitations that should be considered when interpreting the results (Table 1 for studies that reported incidence rates and Table 2 for studies that reported prevalence), most investigations were scored as moderate quality based on an assessment using a standardized tool (the JBI prevalence studies quality assessment tool) (Appendix 4). Nearly all studies included in the SLR were susceptible to potential selection bias in the patient population evaluated. In many cases, this was due to use of a clinic-based registry (such as the T1D Exchange Clinic Registry or the DPV database),[11, 22, 27, 29, 33, 36-38, 40] which may not be representative of a broader population-based cohort of T1D patients; in addition, findings from investigations based on patients

recruited from a single center [23, 28, 35, 39, 41, 43] may not be generalizable to a wider group of T1D patients. No studies were identified by this review that utilized an unselected population-based approach to recruit subjects, such as surveys based on population census data.

Many studies included in this SLR did not provide sufficient information to make a clear determination of study quality for some aspects of study design; this lack of detail was particularly notable for ascertainment of cases of T1D. Only two studies [33, 42] included any description of criteria for the diagnosis of T1D. Of these two, the Chinese study [42] refers to American Diabetes Association and World Health Organization guidelines for diagnosis but does not explicitly state the criteria used to determine T1D cases. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult. When insufficient details were provided to permit assessment of a given study quality parameter, the study was given an "unclear" rating for that aspect of study quality.

Regarding the definition or method of determination of DKA events, there was little consensus among the included studies. Several publications (for example, those based on the T1D Exchange Clinic Registry [11, 22, 29, 33, 36-38]) relied on patient recall of past DKA events. Many studies evaluated DKA events as recorded in hospital/medical records (note that some of these studies utilized patient report of hospitalization),[11, 20-22, 27-29, 36-38, 40, 42] while other investigations did not require hospitalization as part of the definition of DKA or suggested the patient required intravenous fluid or insulin infusion without specifically stating a requirement for hospitalization.[23, 41, 43] Interestingly, three publications [11, 22, 29] based on the T1D Exchange Clinic Registry did a direct comparison of frequency of DKA events based on patient self-report versus medical record extraction and, in each case, found that the number of events was higher for

patient self-reporting than was captured in the patients' medical records. The authors suggested that DKA may be underreported in clinical records and, therefore, chose to use patient self-reported data for further analyses.

While most studies were rated as having moderate study quality based on the JBI prevalence studies quality assessment checklist (Appendix 4), a few outliers were identified with both high and low quality. Most of the studies that scored highly on the quality assessment [11, 20, 21, 27, 40] did so because they provided additional information and details not available in other publications. For example, a study of the DPV database evaluating the impact of physical activity on diabetes outcomes [27] reported a direct comparison of baseline characteristics of patients included in the analysis and those excluded due to missing data, to rule out a significant impact of selection bias in this study. Similarly, as mentioned above, in Weinstock (2013) [11] the authors included two sets of analyses using data for DKA events based on patient self-report and patients' medical records in an attempt to address the limitation of patient recall in determining the frequency of the DKA outcome. In contrast, studies that received lower quality ratings provided incomplete or conflicting information that made it difficult to evaluate the results.[35, 39, 41] In a single-center study conducted in Colorado (US),[35] ascertainment of T1D cases and definition of DKA were not reported, the study period and denominator for calculation of prevalence or incidence were unclear, and the sample size was relatively small (515 patients). Likewise, in a single-center cohort study performed in Slovenia,[39] the definitions for T1D cases, DKA events, and denominator for determination of DKA events were not reported, and the study included only 184 patients. Given the limited data identified in the published literature on the epidemiology of DKA in adults with T1D, even studies that received lower quality ratings were included in this review, to present the totality of the available evidence. In Appendix 4, the notation "Unclear" generally means that insufficient details were provided in the publication to

make an informed determination of study quality for that particular question of the JBI assessment tool.

Discussion

Of the 1,082 citations identified, 19 publications met the inclusion and exclusion criteria for this SLR. Over half of the included studies evaluated patient cohorts based in North America [11, 20-22, 29, 33-38]; data were more limited for studies conducted in Europe [27, 28, 39-41] or elsewhere.[23, 42, 43] Overall, eight studies reported incidence rate, with a range of 0–263 per 1,000 PYs,[23, 27, 28, 34, 35, 39, 42, 43] and 11 studies reported prevalence with a range of 0–128 per 1,000 people.[11, 20-22, 29, 33, 36-38, 40, 41] The lowest incidence rates were reported in Israeli and North American studies [34, 43] and the highest in a Chinese study.[42] The lowest prevalence was reported in a Swedish study [41] and the highest in a Canadian study.[21] No publications reported both incidence rate and prevalence of DKA. Five studies [20, 21, 28, 35, 39] provided sufficiently detailed information to allow for calculation of one of the outcomes of interest when these measures were not directly reported by the study authors. Several publications reported DKA outcome data stratified by age.[11, 22, 33, 36, 38] In contrast, subgroup data for patients categorized based on other baseline characteristics, such as sex,[11] ethnicity,[11] or insulin delivery method,[11, 36] were scarce. While there was considerable variation in study design and data sources among the studies included in the SLR, the majority of investigations presented recently obtained data (within the previous 10 years), and patient baseline characteristics were broadly similar. Many studies were cross-sectional in design or were identified as cross-sectional by the study authors, particularly those examining large (>10,000) patient databases [22, 27, 33, 36, 38]; the few studies that followed patients longitudinally tended to be single-center and to have small (<200) sample sizes.[28, 39, 41] Based on the limited available data, prevalence and incidence rates for DKA were broadly similar across geographic regions but did differ for specific subgroups of patients.

Most studies included in this SLR were assessed as being of moderate quality. Nearly all studies in the review were susceptible to potential selection bias in the included patient population or were of limited generalizability. In addition, many included studies did not provide sufficient information to make a clear determination of quality for some aspects of study design; this lack of detail was particularly notable for ascertainment of cases of T1D. Furthermore, many publications did not describe whether (or how) the included patient cohort differed from the broader population of adults with T1D, which makes an evaluation of potential selection bias, and generalizability, more difficult.

There was little consensus among the included studies regarding the definition of, or method to determine, DKA events. One of the main issues affecting the quality determination for many of the included studies is the fact that the epidemiology of DKA events was not a primary (or, in many cases, even a secondary) objective of the study; rather, DKA data were reported only as part of overall rates of acute diabetic complications (along with other parameters such as severe hypoglycemic events). This may contribute to the lack of detailed descriptions of DKA events. The findings from the Chinese study highlight the difficulties encountered in comparing the epidemiological data across the included studies, in which the methods of calculating incidence rate or prevalence often were not explicitly described. In particular, calculations of incidence rate are challenging without complete information on the patient numerator, given that a single patient can experience multiple recurrent DKA events; it is important to determine whether the incidence rate refers to the number of discrete episodes of DKA or to the number of patients who experienced a DKA event. Most studies [11, 20-22, 29, 33, 35-41] (13 of 19) reported the percentage of patients who had experienced at least one DKA episode (or two or more episodes [28]) over a given study period, rather than the total number of DKA events. In other cases, data were aggregated as cumulative sums of DKA events during the study period[27] or reported as events

per patient per year,[43] and some studies[23, 34, 42, 43] did not provide details regarding the method of calculation of incidence rates.

To our knowledge, this is the first SLR on the epidemiology of DKA in adults with T1D. The strength of this study is the strict delineation that was taken to appropriately assess epidemiology data specifically in adults with T1D. Of note, both young adults and elderly patients were included in this SLR, so the results could be applicable across the whole spectrum of the adult population. Many (24) studies were omitted from the SLR based on the inability to stratify adult data separately from pediatric and/or adolescents or T1D data from a combined population of patients with T1D and T2D.

This review, like any SLR, is subject to limitations that should be considered when interpreting the results. All SLRs are subject to publication bias, as an SLR inherently relies upon data available in the published literature.[32] While a few studies were identified by this SLR that reported findings that did not support one of the authors' primary hypotheses (eg, in Butalia 2014,[21] driving distance to outpatient care was not associated with diabetic outcomes; in Wong 2014,[38] there was no significant association between use of continuous glucose monitoring and DKA events among adult T1D patients), it is likely that null results may be infrequently published. In addition, only data from studies published in English were included in the SLR. This restriction may limit the available data from certain geographic regions in which English is not the primary language of publication and limits the overall scope of the review. As part of the abstract review process, the authors identified non-English studies (which had English abstracts available for review) and found fewer than 10 studies that had the potential for inclusion in the SLR, with data from Japan, China, Bulgaria, Senegal, and the Ivory Coast. Similarly, studies of fewer than 50 adult patients with T1D were excluded. This restriction was deemed reasonable given the epidemiological outcomes of interest (prevalence and incidence rate), as deriving

these values from a very small patient population would lead to a high degree of uncertainty in the estimates. However, it is likely that relevant data for smaller cohorts of patients may not have been included due to this restriction. This SLR was originally intended to include only population-based studies but was expanded to include clinic-based and (potentially unrepresentative) registry studies since there were so few population-based studies found. The small number of studies identified by the review limits the interpretation of comparisons within or between geographic regions and subgroups defined by patient clinical characteristics.

Of note, although the authors acknowledge the availability of nationwide population-based databases with high ascertainment rates in the Nordic countries, which could be used to evaluate epidemiologic queries in T1D, publications on DKA rates among adults in this region were very limited; only one such study [41] met the inclusion criteria for this SLR. Two additional studies of potential interest were identified but ultimately excluded from this review; an epidemiology study based on Denmark public health registries reported the incidence of DKA in the general population and not just among patients with T1D and was thus excluded from the SLR.[44] A study from Sweden reported an incidence rate for DKA of 5.9 per 100,000 people with T1D but defined adults as ≥15 years of age; since this SLR strictly evaluated patients ≥18 years of age, the study was excluded.[45] Similarly, two additional publications [46, 47] reporting data on DKA incidence or prevalence based on patients in the UK were excluded from this review due to lack of patient demographic information; neither study provided sufficient details to allow determination of the patient age range and therefore may have included data for pediatric T1D patients. Based on hospital records in Leicestershire, England, [46] the prevalence of DKA could be calculated as 13.7 per 1,000 people over the two-year study period. An investigation of T1D patients in Scotland [47] found that the cumulative incidence of DKA events was 154 events per 1,000 people for the overall population, with considerable variation based on patients' economic status.

The wide range of incidence rates and prevalence of DKA in adults with T1D [23, 27, 28, 34, 35, 39, 42, 43] is similar to the published literature for children. The incidence of DKA in children with T1D (aged 0–18 years) was lowest in Sweden (15 per 1,000 PY) and highest in the US (80–150 per 1,000 PY; children aged 0–19 years) prior to the Diabetes Control and Complications Trial (DCCT), based on a summary of the epidemiological literature at the time.[48] After raised awareness associated with the DCCT, the incidence of DKA in children with T1D (aged 13–17 years) was 47 per 1,000 PY with conventional therapy compared to 28 per 1,000 PY with intensive therapy.[48] Whereas adults with T1D have decreasing prevalence of DKA with increasing age,[11] an opposite relationship may exist in children. In subgroup analyses of children with T1D, incidence of DKA increased with age for girls (40 per 1,000 PY in girls <7 years of age; 80 per 1,000 PY in girls 7–12 years of age; 120 per 1,000 PY in girls ≥13 years of age, P<0.001 for trend) but not for boys (70 per 1,000 PY in boys <7 years of age; 50 per 1,000 PY in boys 7–12 years of age; 80 per 1,000 PY in boys ≥13 years of age).[48] This suggests a plateau effect for risk of DKA, particularly in females. Rewers and colleagues[48] indicated that the increased risk of DKA among adolescent girls (relative to younger children) may be related to body image issues that lead adolescent girls to skip insulin injections to promote weight loss. Increased insulin resistance due to puberty or obesity may also play a role in greater risk of DKA, as higher insulin dose was a predictor of DKA at all ages. Eating disorders, frequent among children with diabetes, also may affect risk of DKA but may be challenging to identify in this population.[48] In one study using the Diabetes Audit and Research in Tayside Scotland (DARTS) database, it was suggested that poor adherence to insulin treatment in young adults with insulin-dependent diabetes mellitus (IDDM) is the major factor that contributes to long-term poor glycemic control and diabetic ketoacidosis.[49]

Similar to adults with T1D,[11] the prevalence of DKA is higher in non-white versus white ethnicities in children. Non-Hispanic black children with T1D have the highest rate of DKA (23%)

compared to Hispanic children (12%) and non-Hispanic white children (7%).[50] Also similar to adults,[11] the risk of DKA increases in children with psychiatric disorders, those who are underinsured, and those who have uncontrolled HbA1c.[48]

Given the above limitations of many of the available publications, there is a clear need for future investigations to better elucidate the epidemiology of DKA among adult patients with T1D. For future studies, it will be important to clearly describe how cases of T1D are identified and to utilize a standardized definition of DKA, as both of these factors are weaknesses of the currently available evidence. Ideally, future studies would focus specifically on DKA outcomes and employ population-based methods to identify T1D patients and would therefore be more representative of a broad, unselected patient population. It would also be advisable to utilize data from some of the existing large, multicenter, clinic-based registries, such as the US-based T1D Exchange Clinic Registry,[11, 22, 29, 33, 36-38], Nordic databases, the Clinical Practice Research Datalink (CPRD) in the UK, and the German/Austrian DPV,[27, 40] to evaluate large cohorts of patients longitudinally to attempt to confirm some of the associations that have been suggested by cross-sectional analyses of these databases and to identify any changes in DKA trends over time. Since 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. In addition, since DKA is a potentially life-threatening complication and there are currently limited data available on the mortality rates of DKA in a general T1D population, the existing large data sources in the US and Europe could be used to describe DKA-related mortality.

Conclusions

This SLR is, to our knowledge, the first review to describe the epidemiology of DKA among adult patients with T1D. The review identified a limited number of relevant studies; most data were from clinic-based registries of selected patient populations, and most patient cohorts were based in North America. Patient subgroup data were very limited, but a general trend was observed for decreasing prevalence of DKA with increasing patient age. Several other factors, such as lower socioeconomic status, poor glycemic control, female sex, and depression or psychiatric symptoms, were associated with increased risk of DKA. There is a clear need for future studies to better describe the epidemiology of DKA among adult T1D patients. From the currently available body of evidence, which provides an overall prevalence of DKA ranging from approximately 50 to 100 events per 1,000 adult patients with T1D, it is clear that there remains an unmet need to address the prevention of this serious complication.

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Contributors: Brett A Maiese (BAM), Erika Wissinger (EW), Soulmaz Fazeli Farsani (SFF) conceived and designed the study. EW and BAM undertook the literature search, assessed studies for eligibility, and extracted data. In case of disagreement SFF checked the study. BAM, EW, SFF, Kimberly Brodovicz (KB), Nima Soleymanlou (NS), and Jan Marquard (JM) discussed the data, interpreted the results, reviewed the manuscript and revised it critically. NS and JM provided clinical input. All authors approved the final version and take full responsibility for the integrity of the data and the accuracy of the data summarization and interpretation.

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FIGURES, TABLES, and APPENDICES:

Figure 1. Literature Selection and Review Process

Submitted as image.

Footnotes:

Key: SLR = systematic literature review; T1D = type 1 diabetes mellitus.

Key Search Terms: Type 1 diabetes; adult; diabetic ketoacidosis.

Figure 2. Incidence Rate per 1,000 PY of DKA in Adults With T1D (Reported in 8 Studies)

Submitted as image.

Footnotes:

Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; F/U = follow-up; PY = person-years; T1D = type 1 diabetes mellitus; UK = United Kingdom; USA = United States of America; yr = year.

*Calculated value based on data contained within publication.

†Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at CSII initiation.

‡Patients who initiated CSII within 1 year of diagnosis, aged >19 yrs at last visit.

‖Conventional treatment arm from DCCT.

§Intensive treatment arm from DCCT.

¶Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at CSII initiation.

**Patients who initiated CSII at least 1 year post-diagnosis, aged >19 yrs at last visit.

Figure 3. Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies)

Submitted as image.

Footnotes:

Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; HbA1c = glycosylated hemoglobin; MDI = multiple daily injection; NR = not reported; T1D = type 1 diabetes mellitus; yrs = years.

*CGM non-user.

†Calculated value based on data contained within publication.

‡CGM user.

§Overall study population.

‖Definite T1D.

Table 1. Summary of Study Limitations for Studies Reporting Incidence Rate of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Bohn 2015[27] **JBI Score: 9**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all receiving "routine care"	Total population with physical activity data in the DPV	Information bias: low Selection bias: unclear
Bryden 2003[28] **JBI Score: 7**	Longitudinal single-center cohort	NS	89% (initially), with 87 of the 113 patients included at follow-up	All cases were based on hospitalization, likely low	Unclear; patients from 1 specialist care clinic. Only data for patients with recurrent DKA admissions were reported	All follow-up person-time in the cohort	Information bias: low Selection bias: possible
Garg 2004[35] **JBI Score: 1**	Clinic-based single-center registry	NS	N/A (single-center medical record data)	Authors state use of definition from the DCCT Group (unclear potential)†	Unclear; patients all treated at 1 specialty diabetes clinic	Unclear; 515 patients on whom they pulled data	Information bias: low Selection bias: possible
Janez 2012[39] **JBI Score: 0**	Clinic-based single-center registry	NS	N/A (single-center registry/database data)	NS; misclassification potential unclear; data from medical records (not self-report)	Unclear; patients are all treated at 1 specialty diabetes clinic	Unclear; 184 patients on whom they pulled data	Information bias: low Selection bias: possible
Lebenthal 2012[23] **JBI Score: 6**	Clinic-based registry	NS	N/A (clinic-based patient data)	Standardized, likely low	Unclear; patients are all from 1 clinical center	Unclear	Information bias: low (but missing data) Selection bias: unclear
Li 2014[42] **JBI Score: 6**	Longitudinal assessment of patients referred from 16 tertiary care hospitals in 1 province	NS	N/A (patient medical records)	Standardized/criteria-based definition, but data on DKA came from questionnaires (unclear potential)	Unclear; patients are all from tertiary hospitals in 1 Chinese province	NS; likely the entire study population	Information bias: unclear Selection bias: unclear

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Nathan 2009[34] **JBI Score: 7**	DCCT/EDIC (initially an RCT; converted almost all patients to a cohort study design); EDC is a cohort study	NS for either DCCT/EDIC or EDC	NS for DCCT, but 96% of trial participants agreed to participate in EDIC NS for EDC	NS for either cohort. The DCCT/EDIC has both self-reported and clinic-measured variables (method of DKA assessment not stated); unclear potential	Initial cohort for DCCT/EDIC was selected for an RCT, increasing likelihood that patients may not reflect the broader T1D population. For EDC, authors state participants were representative of T1D population of Allegheny County, PA	Unclear	Information bias: low Selection bias: low
Shalitin 2012[43] **JBI Score: 6**	Tertiary care university hospital-based study	NS	N/A (single-center patient medical records)	Highly specific definition based on medical records; likely low	Unclear; patients were treated at a specialized tertiary care center	Unclear, but authors state there was up to 7 yrs of follow-up data on patients after CSII initiation	Information bias: low Selection bias: low

Key: CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; JBI = Joanne Briggs Institute; N/A = not applicable; NS = not stated; PA = Pennsylvania; RCT = randomized controlled trial; T1D = type 1 diabetes mellitus; yr = year.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9. In this manuscript, for the purposes of ease of discussion, a descriptive quality rating of "high" was given to studies with 8 or more Yes responses, and a descriptive quality rating of "low" was given to studies with 3 or fewer "Yes" responses. Studies with more than 3 and fewer than 8 "Yes" responses were described as "moderate" quality.

†The study authors cite this source: *N Engl J Med.* 1993 Sep 30;329(14):977-986; however, upon review, the source did not describe definition of DKA in the DCCT, nor did a high-level Internet search.

Table 2. Summary of Study Limitations for Studies Reporting Prevalence of DKA

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Beck 2012[33] **JBI Score: 7**	Clinic-based registry	Stratified data provided for patients with confirmed T1D†	Very good	Self-report, potential for misclassification	Patient treated by endocrinologists	All patients in registry during specific study time period	Information bias: yes (past events) Selection bias: possible
Butalia 2013[20] **Butalia 2014**[21] **JBI Score: 8**	Linked database analysis	NS	N/A (used linked database data)	Valid; based on hospitalization	Unclear	Patients in the Diabetes, Hypertension and Cholesterol Centre database (2 centers)	Information bias: low Selection bias: possible
Cengiz 2013[22] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-reported hospitalization)‡	Patients treated by endocrinologists	All patients meeting age and disease duration requirements during study time period	Information bias: yes (past events) Selection bias: possible
Laimer 2016[40] **JBI Score: 9**	Clinic-based registry	NS	N/A (used clinic-based patient data)	Standardized, likely low	Unclear	Unclear why this is such a small subset of the overall DPV database population	Information bias: low Selection bias: unclear
Miller 2015[36] **JBI Score: 7**	Clinic-based registry	Not explicitly described	N/S	Likely (self-report); only reported for prior 3 months	Patients all treated by endocrinologists§	All patients in registry during study period who had DKA data from a web-based questionnaire	Information bias: possible (past events) Selection bias: possible
Simmons 2013[37] **JBI Score: 7**	Clinic-based registry	Not explicitly described in this publication	Not stated in this publication	Likely (self-report)	Patients are all treated by endocrinologists, which may introduce some selection bias	Did not include patients with missing data on type of insulin administration or users of real-time CGM	Information bias: possible (past events) Selection bias: possible

Reference and Quality Score*	Study Design	Ascertainment of T1D	Response Rate	DKA Definition (Potential for Misclassification)	Representativeness	Denominator	Likelihood of Potential Biases
Sparud-Lundin 2008[41] **JBI Score: 3**	Clinic-based study	Not stated	86% of potential participants were included; 79% longitudinally followed	Relied on pH value, could be misclassified. 11.5% of the DKA values were missing at the latest time point	Patients all treated at 1 pediatric diabetes clinic and then had to be treated at 1 of 6 adult clinics	Unclear, assumed to be age-specific patient groups (not person-time)[‖]	Information bias: low Selection bias: possible
Trief 2014[29] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS; this analysis only includes patients with PHQ-8 data[‖]	Yes (self-reported hospitalization)[‡]; only reported for prior 3 months	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period who had PHQ-8 data	Information bias: possible (past events) Selection bias: possible
Weinstock 2013[11] **JBI Score: 8**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during study period	Information bias: possible (past events) Selection bias: possible
Wong 2014[38] **JBI Score: 7**	Clinic-based registry	Not explicitly described	NS	Yes (self-reported hospitalization)	Patients all treated by endocrinologists	All patients in registry (meeting age and duration of T1D requirements) during specific study time period	Information bias: possible (past events) Selection bias: possible

Key: CGM = continuous glucose monitoring; DKA = diabetic ketoacidosis; DPV = Diabetes-Patienten-Verlaufsdokumentation; JBI = Joanna Briggs Institute; N/A = not applicable; NS = not stated; PHQ-8 = Patient Health Questionnaire-8 response; T1D = type 1 diabetes mellitus.

*Quality score is based on the total number of "Yes" responses on the JBI Quality Assessment tool for each study. Potential quality scores range from a low of 0 to a high of 9.

[†]Confirmation of T1D diagnosis was problematic for some adult-onset patients with incomplete clinical data; therefore, this group of patients may include some adults with T2D who were misdiagnosed with T1D.

[‡]The frequency of DKA occurrence reported by the clinics from medical record extraction was lower compared to patients' self-report of DKA events.

[§]The authors mention that "uninsured individuals are likely underrepresented in the cohort and pump use may be higher than it is in the overall population of type 1 diabetes in the US".

[‖]PHQ-8 is an 8-item questionnaire that was given at the 1-year data collection point to participants aged ≥18 years.

Appendix 1. Search Strategy Protocol

Submitted as supplementary file.

Appendix 2. Incidence and Prevalence of DKA

Submitted as supplementary file.

Appendix 3. DKA Risk Factors and Associations

Submitted as supplementary file.

Appendix 4. Quality Assessment of Included Studies (JBI Prevalence Studies Checklist)

Submitted as supplementary file.

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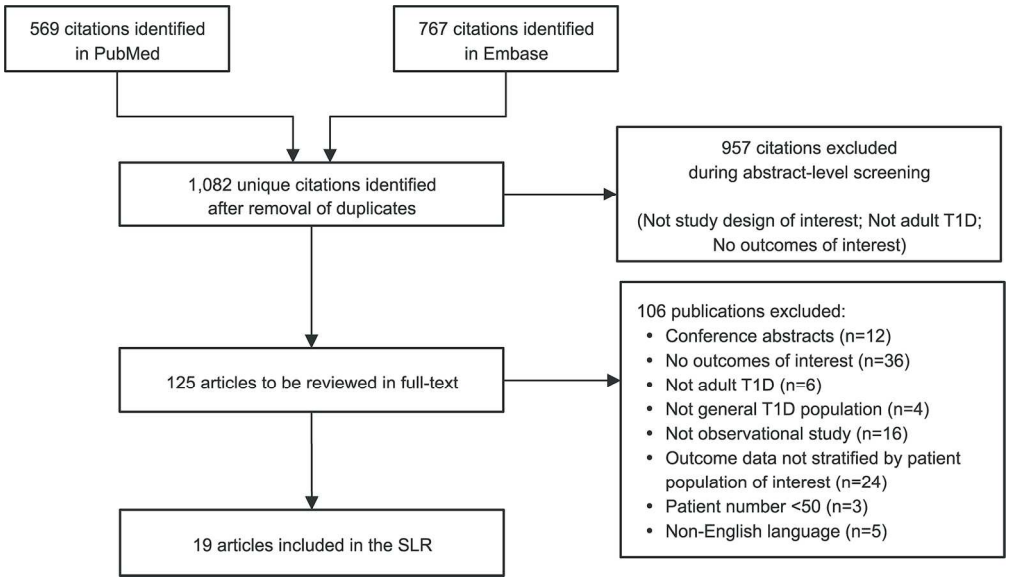

Figure 1. Literature Selection and Review Process

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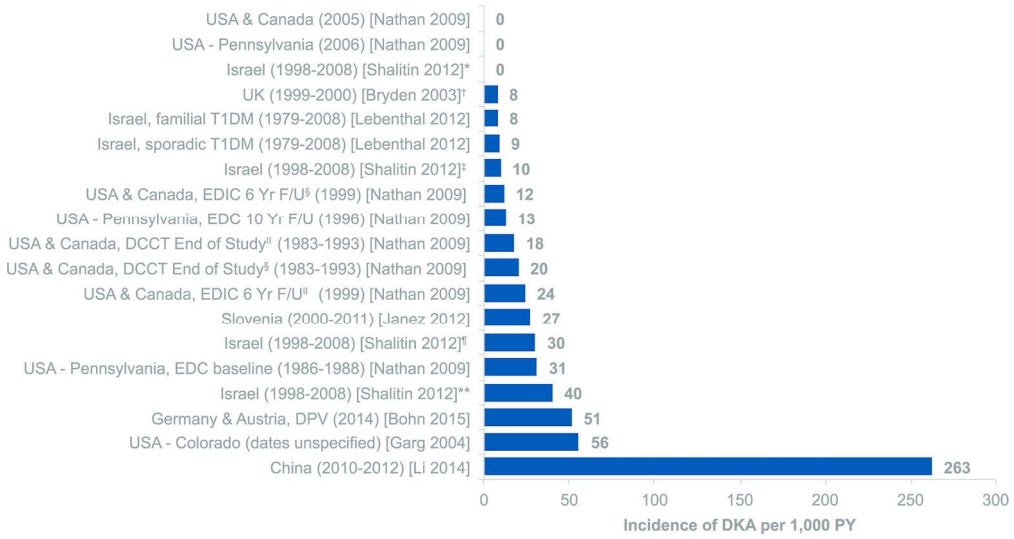

Figure 2. Incidence Rate per 1,000 PY of DKA in Adults With T1D (Reported in 8 Studies)

169x89mm (300 x 300 DPI)

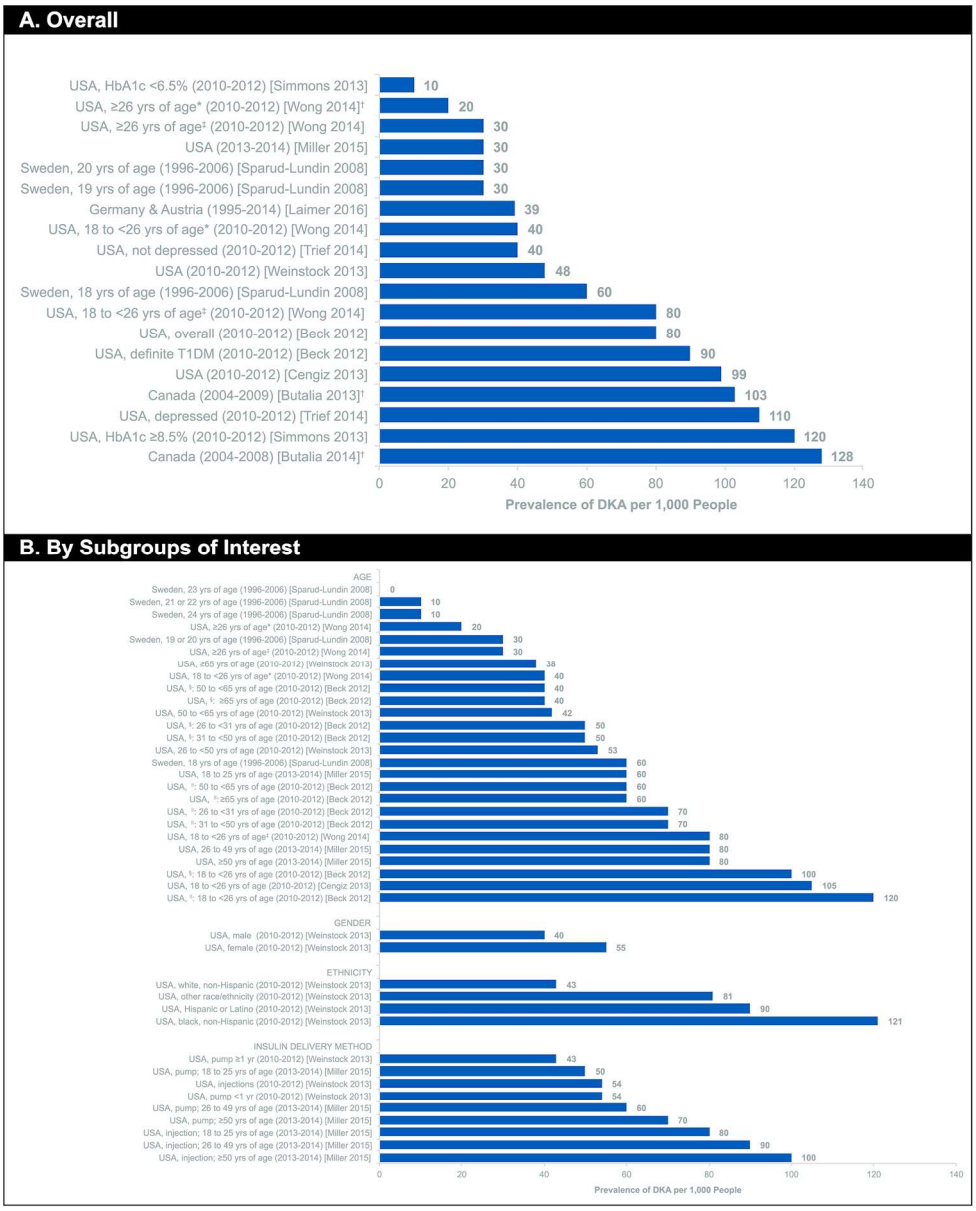

Figure 3. Prevalence (per 1,000 People) of DKA in Adults With T1D (Reported in 11 Studies)

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Systematic Literature Review of the Incidence and Prevalence of Diabetic Ketoacidosis among Adults with Type 1 Diabetes

Search Strategy, v2 (FINAL)

Prepared for:

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June 27, 2016

Xcenda AmerisourceBergen

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TABLE OF CONTENTS

1.0 INTRODUCTION

Boehringer Ingelheim (BI) GmbH seeks to better understand the available published data describing the incidence and prevalence of diabetic ketoacidosis (DKA) in adults with type 1 diabetes mellitus (T1DM), including any relevant epidemiological data reported for stratified patient subgroups (such as by age, gender, geographic location, ethnicity, or typical method of insulin administration). To achieve this, Xcenda will perform a systematic literature review (SLR) which will follow the processes outlined within this study protocol.

The purpose of this protocol is to prospectively define the specific parameters by which the SLR of the incidence and prevalence of DKA in adults with T1DM will be conducted. Once agreed to by all parties, Xcenda will follow this protocol for all aspects of the review. Any changes made after agreement may impact the final research findings, associated project fees, and timeline. A change log of protocol amendments is located in Appendix A.

2.0 KEY RESEARCH QUESTIONS

This study will seek to answer the following key question and related query:

1. What is the overall incidence and prevalence of DKA in adult patients (≥ 18 years, including elderly patients) with T1DM?
    a. What is the incidence and prevalence of DKA in adult T1DM patients by subgroups (when reported in the manuscript and if possible to determine), including: age, gender, geographic location, ethnicity, type of insulin administration (insulin pumps versus injections)?

3.0 SEARCH STRATEGY

The overall approach to the search is outlined below. Additional features of the search strategy and search terms are further detailed in Section 5.0.

3.1 Data Sources

- MEDLINE (via PubMed)
- Embase

3.2 Search Filters and Limitations

3.2.1 Timeframe

- Studies published between January 1, 2000 and the date of the search will be included

3.2.2 Language and Countries

- Language: English only[1]
- Geography: no geographic limitations will be applied, but areas of greatest interest include North and South America, Europe, Japan, Taiwan, and Australia.

[1] Articles that appear relevant but are not published in English will be noted during screening and citations will be provided to BI for review.

3.2.3 Humans

- Only studies conducted in humans will be identified by the search.

3.2.4 Publication Status

- Published studies will be considered; conference abstracts will not be included in the review.

4.0 STUDY SELECTION CRITERIA

4.1 Population

- Adult (≥18 years) patients with T1DM
  - Elderly patients will be included
  - Studies of mixed populations (pediatric and adult, and/or type 1 and type 2 diabetes) will be included if stratified data are reported for adult T1DM patients. These publications will be categorized in a separate table.

4.2 Interventions/Comparators

The SLR will include all T1DM patients, regardless of treatment. Type of insulin and route of administration are of particular interest and will be captured when these data are available in the literature.

4.3 Outcomes

- Study endpoints (for overall patient population and relevant subgroups)
  - Incidence of DKA
  - Prevalence of DKA

4.4 Study Design

Included study designs:

- Population-based observational studies
- SLRs and meta-analyses[2]

Excluded study designs:

- Randomized controlled trials / clinical trials
- Pharmacokinetic and pharmacodynamic studies
- Non-randomized interventional studies
- Preclinical or animal studies
- Editorials, letters, and commentaries
- Case studies, reports, or case series

[2] Reference lists of SLRs will be hand-searched for any articles that may have been missed by the database search. If additional studies are identified (published from 2000 onwards), the data from those studies will be extracted separately. Data extraction for SLRs will only include a basic summary of the study design and overall results.

- Theses and dissertations
- Narrative literature reviews
- Small studies (n<50)
- Guidelines

5.0 SEARCH TERMS

Table 5-1 outlines the search terms to be considered as well as specific details on the search strategy.

Table 5-1. Search Strategy (with Sample Searches in MEDLINE and Embase)

Database	MEDLINE (via PubMed)	
Search Limitations or Filters Applied	Publication dates: 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	(((((((diabetes mellitus, type 1[MeSH Terms]) OR type 1 diabetes[Title/Abstract]) OR juvenile onset diabetes[Title/Abstract]) OR brittle diabetes[Title/Abstract]) OR insulin dependent diabetes[Title/Abstract]) OR iddm[Title/Abstract]) OR autoimmune diabetes[Title/Abstract]) OR sudden onset diabetes[Title/Abstract]	85,033
#2	(((diabetic ketoacidosis[MeSH Terms]) OR diabetic ketoacidosis) OR diabetic acidosis) OR diabetic ketosis	8,267
#3	((((adult[MeSH Terms]) OR adult) OR young adult) OR middle age) OR elderly	6,589,216
#4	#1 AND #2 AND #3	1,265
#5	review NOT (systematic OR (meta AND analys*))	2,372,581
#6	#4 NOT #5	1131
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**596**

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#1	'diabetes mellitus, type 1'/exp OR 'type 1 diabetes mellitus':ab,ti OR 'juvenile onset diabetes':ab,ti OR 'brittle diabetes':ab,ti OR 'insulin dependent diabetes':ab,ti OR iddm:ab,ti OR 'autoimmune diabetes':ab,ti OR 'sudden onset diabetes':ab,ti	106,633

Database	Embase	
Search Limitations or Filters Applied	Publication date from 2000/01/01 to 2016/06/23; Humans	
Date of Search	June 23, 2016	
Search	**Query**	**Number of records found**
#2	'diabetic ketoacidosis'/exp OR 'diabetic acidosis'/exp OR 'diabetic ketosis'/exp	9,093
#3	'adult'/exp OR 'young adult'/exp OR 'middle age'/exp OR 'elderly'/exp	6,066,920
#4	#1 AND #2 AND #3	1,078
#5	review NOT (systematic OR (meta AND analys*))	3,002,962
#6	#4 NOT #5	950
#7	Filters applied: Publication date from 2000/01/01 to 2016/12/31; Humans	**766**

6.0 DATA EXTRACTION

Data extraction will be conducted in MS Excel and converted into MS Word tables for the final report. The elements for data extraction are outlined in Table 6-1.

Table 6-1. Example Data Extraction Templates

Author, year	Country	Type of study	Study period	Definition of DKA	Guidelines used for defining DKA	T1DM cases were identified based on?	Study participants				
							Mean, median, and range of age (as available)	Male%	Inclusion/ exclusion criteria	Sample size	Ethnicity

Author, year	Type of insulin	Insulin pump (Y/N)	Follow up years	N of new cases of DKA	Denominator for calculating rates of DKA	INC of DKA per 1000 PY	PREV of DKA per 1000 people	Conclusions	Notes/Comments/study limitations

APPENDIX A: PROTOCOL CHANGE LOG

Date	Protocol Section	Amendment	Status
Date of change	*Section X*	*Description of change*	*Completed Y/N*
8 July 2016	Section 6.0 Data Extraction	Additional DKA-related data (specifically potential risk factors associated with DKA) as reported in the included studies will be captured during data extraction.	Y

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
US and Canada								
Beck 2012[35]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	25,833*	NR	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 80† Definite T1D: 90
Butalia 2013[22]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, and census in Canada	1,994	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	127.9‡
Butalia 2014[23]	Data linkage study combining clinical and administrative health data	T1D patient database, inpatient discharge database, kidney disease laboratory data, census, and database of postal codes in Canada	1,467	DKA hospitalization was identified using the ICD-10-CA. The relevant codes included E10.100, E10.101, E10.120, E10.121, E10.10 and E10.12	Based on hospitalization records	Number of patients with and without a DKA hospitalization over the study period	NR	102.9‡
Cengiz 2013[24]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	13,487 DKA subset, n=13,005 Aged 18 to <26 yrs subset, n=3,624	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 99
Garg 2004[37]	Retrospective analysis from a single center	Electronic patient record system in US	515	NR	Patient medical records	Number of patients who had a DKA event over the study period	Cumulative incidence: 55.6‡	NR
Miller 2015[38]	Prospective, multicenter, clinic-based patient registry	T1D Exchange Clinic Registry in US	16,061* DKA subset, n=2,561	Participant-reported DKA diagnosed by a doctor that required treatment in a	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Overall: 30

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
				healthcare facility				
Nathan 2009[36]	Observational, longitudinal cohort study	EDIC study (extension of DCCT in Canada and US) EDC study in US	***Conventional treatment*** DCCT, n=730 EDIC, n=606 ***Intensive treatment*** DCCT, n=711 EDIC, n=620 ***EDC*** Baseline, n=161; Year 10, n=105; Year 18, n=88	NR	NR	Incidence rate per 1,000 PY	***Conventional treatment*** DCCT: 18 EDIC Year 6: 24 EDIC Year 12: 0 ***Intensive treatment*** DCCT: 20 EDIC Year 6: 12 EDIC Year 12: 0 ***EDC*** Baseline: 31 Year 10: 13 Year 18: 9	NR
Simmons 2013[39]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	1,894	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Excellent HbA1c control (<6.5%): 10 Fair/poor HbA1c control (≥8.5%): 120
Trief 2014[31]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	6,172	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	Depressed: 110 Non-depressed: 40
Weinstock 2013[13]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	7,012 DKA subset, n=6,796	Patient-reported overnight hospitalization for DKA Clinic-documented hyperglycemia and symptoms such as polyuria, polydipsia, nausea, or vomiting; serum ketones or large/moderate urine ketones; arterial blood pH <7.30, or venous pH	Patient self-report via questionnaire (these data were used for all primary analyses)	Percent of patients with at least 1 DKA event in the prior 12 months	NR	Overall: 48

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
				<7.30, or serum bicarbonate <15 mmol/L; and treatment provided in a healthcare facility				
Wong 2014[40]	Cross-sectional analysis of a prospective clinic-based patient registry	T1D Exchange Clinic Registry in US	17,317*	Patient-reported overnight hospitalization for DKA	Patient self-report via questionnaire	Percent of patients with at least 1 DKA event in the prior 3 months	NR	***18 to <26 yrs*** CGM user: 80 CGM non-user: 40 ***≥26 yrs*** CGM user: 30 CGM non-user: 20
Europe								
Bohn 2015[29]	Cross-sectional analysis of prospective, clinic-based patient registry	DPV prospective database of T1D patients in Germany and Austria	18,028	pH value <7.3 or hospital admission due to DKA	Patient medical records	DKA events per 100 PY	51.3	NR
Bryden 2003[30]	Single-center longitudinal cohort study	Case register of a young adult diabetic clinic in United Kingdom	113	Hospital admissions for DKA	Patient medical records	Number of patients with ≥2 admissions for DKA over 1,261 PY of follow-up	7.9‡	NR
Janez 2012[41]	Prospective, single-center, clinic-based patient registry	Registry of adult T1D patients treated with CSII in Slovenia	184	NR	Patient medical records	Number of patients with a DKA episode over the study period	Cumulative incidence: 27.2‡	NR
Laimer 2016[42]	Cross-sectional analysis of prospective, clinic-based patient registry	DPV prospective database of T1D patients in Germany and Austria	5,545	Hospital admission due to ketoacidosis with hyperglycemia >11 mmol/L and pH <7.3	Patient medical records	Percentage of patients with a DKA event	NR	39
Sparud-Lundin 2008[43]	Single-center, clinic-based longitudinal cohort study	Diabetes outpatient medical/nursing records from	104	Blood pH <7.30	Patient medical records	Number and percentage of patients with a DKA event for each year (from 18–24 yrs)	NR	Aged 18: 60 Aged 19: 30 Aged 20: 30 Aged 21: 10

Reference	Study Design	Data Source	N	DKA Definition	DKA Ascertainment	DKA Event Description in Publication	Incidence per 1,000 PY	Prevalence per 1,000 People
		age 18–24 yrs in Sweden						Aged 22: 10 Aged 23: 0 Aged 24: 10
Other Regions								
Lebenthal 2012[25]	Retrospective analysis	Medical records from a single center in Israel	452*	Blood pH <7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	DKA events per 100 PY	Familial T1D: 8 Sporadic T1D: 9	NR
Li 2014[44]	Cross-sectional, multicenter, clinic-based study	Patient medical records from 16 tertiary hospitals in China	611*	Hyperglycemia (blood plasma glucose >13.9 mmol/L), blood bicarbonate <15 mmol/L and/or pH <7.30 (arterial), and elevated level of ketones in the urine or blood	Patient medical records; diagnosis based on criteria of the Chinese Diabetes Society, the American Diabetes Association , Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology	DKA events per 100 PY	263	NR
Shalitin 2012[45]	Retrospective analysis of patient medical records from a single center	Medical records from a single center in Israel ***Group 1:*** CSII initiated within 1 year of diagnosis ***Group 2:*** CSII initiated at least 1 year post-diagnosis	488*	Blood pH < 7.3 with bicarbonate <15 mEq/L and need for intravenous fluid and insulin infusion	Patient medical records	Average number of DKA events per patient per year	***Group 1*** >19 yrs at last visit: 10 >19 yrs at CSII initiation: 0 ***Group 2*** >19 yrs at last visit: 40 >19 yrs at CSII initiation: 30	NR

Key: CGM = continuous glucose monitoring; CSII = continuous subcutaneous insulin infusion; DCCT = Diabetes Control and Complications Trial; DKA = diabetic ketoacidosis; EDC = Epidemiology of Diabetes Complications; EDIC = Epidemiology of Diabetes Interventions and Complications; DPV = Diabetes-Patienten-Verlaufsdokumentation; ICD-10-CA = International Classification of Diseases, 10th Revision with Canadian Enhancements; NR = not reported; PY = person-years; SLR = systematic literature review; T1D = type 1 diabetes mellitus; US = United States; yrs = years.

* Overall study population; includes pediatric T1D patients (outcome data not included for pediatric patients).

† The overall patient population includes both definite T1D cases (patients meeting all diagnostic criteria) and probable T1D cases (patients meeting only some of the diagnostic criteria); the results for the definite T1D population were reported separately.

‡ Shaded (gray) cells represent outcome data that were calculated by the authors of this SLR based on the information available in the publication, rather than data directly reported by the study authors. Cumulative incidence was calculated/defined as number of cases out of total study population.

Reference	Methods	Measures of DKA Association/Risk	Comments
Bohn 2015[29]	Multiple Poisson regression models adjusted for age, sex, and diabetes duration, with treatment center as a random factor provided adjusted estimates of the incidence of DKA events per 100 PY: mean (standard error)	Adjusted estimate of DKA events per 100 PY: mean (standard error) Inactive patients (n=11,357): 6.48 (0.03) Patients who were physically active 1–2 times per week (n=3459): 3.99 (0.03) Patients who were physically active >2 times per week (n=3212): 2.40 (0.03)	**A significant inverse association was found between rates of DKA and level of physical activity** for the overall study population and for all subgroups (all *P*<0.0001)
Bryden 2003[30]	Multiple and logistic regression analyses with dependent variables: psychiatric referral, recurrent DKA admissions over the study period, any serious diabetic complication, HbA1c, and psychiatric symptoms at follow-up Independent variables entered into the model at baseline were sex, psychiatric symptoms, HbA1c, duration of diabetes, BMI, number of daily injections, and marital status Sex and baseline psychiatric symptoms were forced into the model, but other covariates that were not statistically significant at the 10% level were excluded from final models	Presence vs absence of psychiatric symptoms at baseline: **OR: 9.1; 95% CI: 2.9 to 28.6; *P*<0.0001** for recurrent admissions for DKA	**Patients with recurrent admissions for DKA over the study period were significantly more likely to have developed diabetic complications at follow-up than patients without recurrent DKA admissions**, and in multiple regression analyses, recurrent admissions for DKA over the study period predicted psychiatric symptoms at follow-up
Butalia 2013[22]	Logistic regression was used to calculate simple bivariate ORs for the associations between the DKA outcome and individual predictor variables. This was then followed by multivariable logistic regression modelling, for which backward elimination was performed to construct a parsimonious prediction model Variable elimination was carried out in thematic groups: the healthcare system, socioeconomic status, comorbidities, diabetes complications, indicators of complications, BMI, age, and sex	In univariate analyses, DKA hospitalization was associated with: Younger age **OR: 0.98 per year; 95% CI: 0.97 to 0.99** Lower BMI **OR: 0.94; 95% CI: 0.92 to 0.97** Shorter duration of T1D **OR: 0.97 per year; 95% CI: 0.96 to 0.98** Use of statin medications lowered the risk of DKA hospitalization **OR: 0.60; 95% CI: 0.42 to 0.86** Several comorbidities and complications were associated with increased risk of DKA hospitalization: Gastroparesis **OR: 3.85; 95% CI: 1.90 to 7.89** Psychiatric diagnosis **OR: 1.90; 95% CI: 1.21 to 2.97** Increased eGFR **OR: 1.12 per 10 mL/min 1.73 m^2; 95% CI: 1.06 to 1.17** Higher HbA1c **OR: 1.29 per 1% increase; 95% CI: 1.20 to 1.39** was associated with DKA hospitalization Higher quartiles of income compared with the lowest quartile (quartile 2, **OR: 0.66; 95% CI: 0.46 to 0.96**; quartile 3, **OR: 0.66; 95% CI: 0.45 to 0.95**; quartile 4: **OR 0.8; 95% CI: 0.68 to 0.96**) and more formal education (**OR: 0.42; 95% CI: 0.18 to 0.97**) lowered the odds of DKA hospitalization In multivariable logistic regression, longer duration of T1D was associated with lower odds of DKA hospitalization (**OR: 0.96 per year; 95% CI: 0.95 to 0.98**). Other factors significantly associated with DKA hospitalization included gastroparesis (**OR: 4.13; 95% CI: 1.82 to 9.35**), psychiatric diagnosis (**OR: 1.98; 95% CI: 1.22 to 3.19**), and higher HbA1c (**OR: 1.25; 95% CI: 1.16 to 1.35**)	

Reference	Methods	Measures of DKA Association/Risk	Comments
Butalia 2014[23]	Multivariate logistic regression analyses were used to assess the association between driving distance from patient residence to outpatient diabetes care sites and the DKA outcome Unadjusted and adjusted models for clinical and sociodemographic factors also were constructed for DKA hospitalization. Clinical factors included BMI, duration of diabetes, specialist care, comorbidities and complications, HbA1c, and eGFR. Other variables included sex, age, median family income, and neighborhood education level (proportion with university degree/diploma/certificate)	In multivariate analyses, driving distance from home to diabetes center 1 (adjusted OR: 1.02 per 1 km; 95% CI: 0.96 to 1.07) to diabetes center 2 (adjusted OR: 1.01; 95% CI: 0.99 to 1.04) or to closest general practitioner (adjusted OR: 0.9; 95% CI: 0.63 to 1.25) was not associated with DKA hospitalization	Patients with DKA hospitalization were younger, had shorter duration of T1D, and had higher HbA1c than patients without DKA hospitalization
Cengiz 2013[*24]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01. Interactions among age, diabetes duration, sex, and HbA1c were evaluated, and no interaction term was significant at the level of 0.01	Detailed data on OR for adjusted and unadjusted models and numerous patient stratifications are available in Table 3 and Supplemental Table 2 of the publication	After adjusting for age, a higher **frequency of DKA was significantly associated with female sex, non-white race, lower income, no private insurance, higher HbA1c, and MDI insulin method (vs pump); (all *P*<0.001).** In a multivariate analysis**, female sex, higher HbA1c, non-white race, lower income, and lack of private insurance continued to be significantly associated with a higher frequency of DKA**. Results were similar for each age group.
Laimer 2016[42]	Linear regression analysis adjusted for age, sex, duration of diabetes, and basal insulin rate per kg body weight was used to analyze the association between basal rate variability and DKA	In male adult T1D patients, a **higher variability index of basal insulin rates was associated with higher frequency of DKA (r=0.04; *P*=0.029)** Logistic regression analysis (adjusted for age, sex, duration of disease, and total basal insulin) **confirmed significant positive correlations of the variability index of basal insulin rates with DKA (β=0.012; *P*=0.017) and between basal insulin rates (basal rate/kg/24h) and DKA (β=1.743; *P*<0.001),** but not with age (β=0.008; *P*=0.159), duration of disease (β=0.001, *P*=0.884), or sex (β=0.205, *P*=0.154) and DKA	
Lebenthal 2012[25]	Multiple logistic regression by stepwise backward methods was applied to determine variables significantly associated with acute complications	Overall rates of DKA events were significantly higher in familial than in sporadic cases (2.8 vs 1.9 events per 100 PY) **IRR=1.5; 95% CI: 1.03 to 2.22; *P*=0.03** Note that this association was not significant for patients aged >19 years (IRR=0.92 [95% CI: 0.36 to 2.32], *P*=0.87)	A higher mean HbA1c level was a predictor for DKA events in both the familial and the sporadic groups, whereas age at diagnosis of T1D and sex did not predict DKA events in either group
Li 2014[44]	A Poisson regression model was used to determine risk factors for secondary DKA. Separate backwards stepwise logistic regression analyses were used to identify risk factors for the recurrence of secondary DKA	Detailed data on relative risk are available in Figure 1 of the publication and results of logistic regression analyses for secondary DKA recurrence are reported in Table 2 For the overall population, the following parameters were significant risk factors for secondary DKA:	There were no significant differences in DKA incidence between patients treated with insulin glargine and patients treated with NPH insulin Regarding recurrences, 34.4% of secondary DKA episodes represented

Reference	Methods	Measures of DKA Association/Risk	Comments
		Female sex (**RR=2.12; 95% CI: 1.50 to 3.04**) Medical reimbursement rates <50% (**RR=1.84; 95% CI: 1.33 to 2.60**) Uncontrolled diet ("never controlled" vs "usually controlled") (**RR=1.76; 95% CI: 1.18 to 2.57**) Smoking (**RR=2.18; 95% CI: 1.30 to 3.59**) Poor glycemic control (HbA1c per1.0% increase, **RR=1.15; 95% CI: 1.10 to 1.21**) An overweight/obese BMI (vs normal) significantly reduced the risk of secondary DKA (**RR=0.57; 95% CI: 0.31 to 0.96**) In logistic regression models, recurrence of secondary DKA was associated significantly with: Female sex (**RR=10.56; 95% CI: 1.97 to 56.72; *P*=0.01**) Smoking (**RR=6.99; 95% CI: 1.02 to 48.00; *P*=0.05**) Poor β cell function (stimulated C-peptide/100 pmol/L decrease (**RR=4.22; 95% CI: 1.20 to 6.97; *P*=0.01**) Poor glycemic control (HbA1c per1.0% increase, (**RR=1.16; 95% CI: 1.00 to 1.34; *P*=0.05**)	recurrent events (≥2 episodes) in 3.8% of the patients
Miller 2015[38]	No statistical modelling analyses reported; qualitative summary data only	NR	The frequency of DKA tended to be higher among participants with higher HbA1c levels and slightly lower among participants using an insulin pump
Shalitin 2012[45]	No statistical modelling analyses reported; summary data only based on Pearson's chi-square test or Fisher's exact test	NR	The rates of DKA episodes were not significantly different between the 2 groups (patients who initiated CSII within 1 year of diagnosis or patients who initiated CSII at least 1 year after diagnosis), either in total or on subanalysis by age groups, pubertal stages, diabetes duration, or CSII treatment duration
Trief 2014[31]	Diabetes-management outcomes (including DKA) in those with and without depression were compared using linear regression for continuous variables and logistic regression models for categorical variables	Compared with non-depressed participants, depressed participants had more frequent DKA events in the past 3 months (**11% vs 4%; *P*<0.001** for all 3 definitions of depression) Compared with lower-scoring participants, participants with higher depression scores were more likely to experience more frequent DKA (***P*<0.001)** NR	

Reference	Methods	Measures of DKA Association/Risk	Comments
Weinstock 2013[13]	Separate logistic regression models were used to evaluate the association between baseline demographic and clinical factors and the occurrence of a DKA event. Factors with a *P*-value <0.10 from individual factor models adjusted for age were included in an initial multivariate model, and then a backward elimination procedure was used to remove variables with a *P*-value ≥0.01	Detailed data on OR and 95% CI from logistic regression models evaluating the association between baseline demographic and clinical characteristics and the occurrence of a patient-reported or clinic-reported DKA event are described for numerous patient subgroup stratifications in Table 2 and Supplemental Table 3 of the publication	Frequency of DKA was lower with increasing age. However, the age effect was largely explained by HbA1c level, which was strongly associated with the occurrence of a DKA event. Frequency of DKA was not associated with diabetes duration In addition to HbA1c level, **a higher frequency of DKA was associated with lower socioeconomic status based on education level, income, and insurance status (*P*<0.001 for each in multivariate model) and female sex (*P*=0.008)**. In univariate models, non-Hispanic black and Hispanic participants had higher frequencies of DKA than non-Hispanic whites, and current smokers had higher frequency of DKA than nonsmokers, but after adjusting for socioeconomic status, neither factor was significant in the multivariate model. Frequency of DKA was not significantly different between pump and injection users
Wong 2014[40]	Logistic regression modelling adjusted for sex, race/ethnicity, education level, annual household income, health insurance status, diabetes duration, and insulin delivery method (pump/ injection)	CGM UYser vs CGM non-user: <u>18 to <26 yrs:</u> Unadjusted OR: 0.5; 95% CI: 0.2 to 1.0; *P*=0.06 Adjusted OR: 0.6; 95% CI: 0.2 to 1.8; *P*=0.33 <u>≥26 yrs:</u> Unadjusted OR: 0.7; 95% CI: 0.4 to 1.1; *P*=0.09 Adjusted OR: 1.4; 95% CI: 0.8 to 2.3; *P*=0.23	CGM use was not significantly associated with rates of DKA for these age groups in logistic regression models

Key: BMI = body mass index; CGM = continuous glucose monitoring; CI = confidence interval; CSII = continuous subcutaneous insulin infusion; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin A1c; IRR = incidence rate ratio; NPH = neutral protamine Hagedorn; NR = not reported; OR = odds ratio; PY = person-years; RR = relative risk; T1D = type 1 diabetes mellitus.

Bold text highlights associations that were found to be statistically significant in each study.

* Associations were calculated based on the full patient population (which included pediatric patients); however, analyses were adjusted for age.

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview N=21 studies	**12 (57%) Yes 7 (33%) Unclear 2 (10%) No**	**17 (81%) Yes 3 (14%) Unclear 1 (5%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**18 (86%) Yes 0 (0%) Unclear 3 (14%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**9 (43%) Yes 12 (57%) Unclear 0 (0%) No**	**11 (52%) Yes 9 (43%) Unclear 1 (5%) No**	**18 (86%) Yes 3 (14%) Unclear 0 (%) No**	**16 (76%) Yes 4 (19%) Unclear 1 (5%) No**
Beck 2012[35]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Bohn 2015[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bryden 2003[30]	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2013[22]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Butalia 2014[23]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cengiz 2013[24]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Garg 2004[37]	Unclear	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear
Janez 2012[41]	No	No	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear
Laimer 2016[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lebenthal 2012[25]	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear
Li 2014[44]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Miller 2015[38]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Nathan 2009[36]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Shalitin 2012[45]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Simmons 2013[39]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study participants and setting described in detail?	Was data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all study participants?	Was the statistical analysis appropriate?	Was the response rate adequate? If no, was the low response rate managed appropriately?
Overview N=21 studies	**12 (57%) Yes 7 (33%) Unclear 2 (10%) No**	**17 (81%) Yes 3 (14%) Unclear 1 (5%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**18 (86%) Yes 0 (0%) Unclear 3 (14%) No**	**15 (71%) Yes 5 (24%) Unclear 1 (5%) No**	**9 (43%) Yes 12 (57%) Unclear 0 (0%) No**	**11 (52%) Yes 9 (43%) Unclear 1 (5%) No**	**18 (86%) Yes 3 (14%) Unclear 0 (%) No**	**16 (76%) Yes 4 (19%) Unclear 1 (5%) No**
Sparud-Lundin 2008[43]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	No
Trief 2014[31]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes
Weinstock 2013[13]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Wong 2014[40]	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

Key: JBI = Joanna Briggs Institute.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9; Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 1 & 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-14; Figs 2 & 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Tables 1 & 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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