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RESEARCH

Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review

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Abstract

Objective To identify the factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults.

Design Systematic review.

Data sources PubMed, EMBASE, Web of Science, Scopus, and Cinahl and article reference lists.

Study selection Cohort studies including unselected groups of children and young adults presenting with new onset type 1 diabetes that distinguished between those who presented in diabetic ketoacidosis and those who did not and included a measurement of either pH or bicarbonate in the definition of diabetic ketoacidosis. There were no restrictions on language of publication.

Results 46 studies involving more than 24 000 children in 31 countries were included. Together they compared 23 different factors. Factors associated with increased risk were younger age (for <2 years old *v* older, odds ratio 3.41 (95% confidence interval 2.54 to 4.59), for <5 years *v* older, odds ratio 1.59 (1.38 to 1.84)), diagnostic error (odds ratio 3.35 (2.35 to 4.79)), ethnic minority, lack of health insurance in the US (odds ratio 3.20 (2.03 to 5.04)), lower body mass index, preceding infection (odds ratio 3.14 (0.94 to 10.47)), and delayed treatment (odds ratio 1.74 (1.10 to 2.77)). Protective factors were having a first degree relative with type 1 diabetes at the time of diagnosis (odds ratio 0.33 (0.08 to 1.26)), higher parental education (odds ratios 0.4 (0.20 to 0.79) and 0.64 (0.43 to 0.94) in two studies), and higher background incidence of type 1 diabetes (correlation coefficient –0.715). The mean duration of symptoms was similar between children presenting with or without diabetic ketoacidosis (16.5 days (standard error 6.2) and 17.1 days (6.0) respectively), and up to 38.8% (285/735) of children who presented with diabetic ketoacidosis had been seen at least once by a doctor before diagnosis.

Conclusions Multiple factors affect the risk of developing diabetic ketoacidosis at the onset of type 1 diabetes in children and young adults, and there is potential time, scope, and opportunity to intervene between symptom onset and development of diabetic ketoacidosis for both parents and clinicians.

Introduction

Type 1 diabetes is one of the most common endocrine diseases in children. Worldwide, an estimated 65 000 children under 15 years old develop the disease each year, and the global incidence in children continues to increase at a rate of 3% a year.[1 2] The current incidence in the UK is around 26/100 000 per year.[3]

Between 10% and 70% of these diagnosed children present in diabetic ketoacidosis, a metabolic derangement characterised by the triad of hyperglycaemia, acidosis, and ketonuria. The current criteria for diagnosis published by the International Society for Paediatric and Adolescent Diabetes is blood glucose >11 mmol/L, venous pH <7.3 or bicarbonate <15 mmol/L, and ketonaemia and ketonuria.[4] It carries a substantial risk of life threatening complications such as cerebral oedema and is the commonest cause of diabetes related death in children.[5] The longer term clinical course of type 1 diabetes also seems to be influenced by it: children with diabetic ketoacidosis at diagnosis have poorer glycaemic control,[6] less residual β cell function up to two years after diagnosis,[7] and a lower frequency of remission.[8 9]

It is unclear why some children present in diabetic ketoacidosis whereas others do not and whether the development of diabetic ketoacidosis is a consequence of delayed diagnosis and treatment or whether it reflects a particularly aggressive form of diabetes.[10] Understanding which factors are associated with diabetic ketoacidosis at diagnosis and the relative importance of delayed diagnosis and treatment is, therefore, important. This potentially informs both our understanding of the disease as well as the development of patient, professional, and population based interventions to reduce the proportion of children presenting in diabetic ketoacidosis. Several individual factors from individual

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studies have been quoted in guidelines and consensus statements.[11-13] To our knowledge, this is the first systematic review of all factors associated with diabetic ketoacidosis at the diagnosis of type 1 diabetes in children and young adults.

Methods

Search strategy

An electronic literature search of PubMed, EMBASE, Web of Science, Scopus, and Cinahl up to March 2011 was performed using a combination of subject headings and free text incorporating "diabetic ketoacidosis" , "diabetes and ketoacidosis" , and "diagnosis" limited to infants, children, or adolescents (see appendix on bmj.com for complete search strategy). The search was then extended by manually screening the reference lists of all included papers.

Study selection

Included studies fulfilled all of the following criteria: published as a primary research paper in a peer reviewed journal; included cohorts of children and young adults presenting with new onset (that is, previously undiagnosed) type 1 diabetes who had not been selected based on other characteristics; distinguished between those children who presented in diabetic ketoacidosis and those who did not; and included a measurement of either pH or bicarbonate in the definition of diabetic ketoacidosis. Studies including only highly selected groups—such as neonates or children being treated with high dose corticosteroids or receiving chemotherapy—as well as drug trials and conference proceedings were excluded. We chose to include all studies which defined diabetic ketoacidosis based on measurement of either pH or bicarbonate as this was an exploratory review not limited by time or language of publication, and we expected a range of different definitions.

One reviewer (JAUS) performed the search and screened the titles and abstracts to exclude papers that were clearly not relevant. A second reviewer (FMW) independently assessed a random selection of papers excluded at that stage. For papers where a definite decision to reject could not be made based on title and abstract alone, the full text was examined. At least two reviewers (JAUS and FMW or MJT) independently assessed all full text papers, and those not meeting the inclusion criteria by both researchers were excluded. Papers in which it was unclear whether the inclusion criteria were met were assessed by a third researcher (MJT or FMW), and where either the definition of diabetic ketoacidosis was not given or we were unable to interpret the data presented adequately we contacted the authors for clarification.

Quality assessment

Quality assessment was conducted independently by at least two reviewers (JAUS and FMW or MJT). We used the Critical Appraisal Skills Programme guidelines for case control and cohort studies[14] as an initial framework and classified each as key paper, satisfactory, unsure, fatally flawed, or irrelevant as in the approach of Dixon-Woods et al.[15] We excluded papers classified as fatally flawed or irrelevant and discussed those classified as unsure at consensus meetings.

Data extraction and synthesis

Characteristics of included studies were extracted; these included period of study, number and type of study centres, study design, methods of recruitment, sample size, age and number of participants, and definition of diabetic ketoacidosis. Using a standardised form to minimise bias, at least two researchers (JAUS and FMW or MJT) independently extracted data on all factors for which there were data available for children presenting both with and without diabetic ketoacidosis. The factors were grouped into individual, family, physician, disease related, and others. Studies reported the effects of risk factors in a variety of ways, and hence various approaches to synthesis were needed. We expressed the effect of a risk factor as an odds ratio with 95% confidence interval where possible, but where the data did not allow this we compared the mean and standard deviation of the risk factor between those individuals with and without diabetic ketoacidosis and expressed this as mean and standard error. When studies recruited children over more than one time period and it was possible to separate all the data into different time periods, we used only the most recent period. In all other cases we combined the data from all time periods.

Statistical methods

Where possible, we combined odds ratios using random effects meta-analysis: data were analysed with Stata (version 11.1), and we assessed heterogeneity between studies using Cochran's Q test and the I^2 statistic.[16 17] Where the mean and standard deviation of the risk factor were compared between those individuals with and without diabetic ketoacidosis, we used a two sample *t* test. Significance was set at $P<0.05$, and 95% confidence intervals are quoted throughout.

Results

After duplicates were removed, the search identified 1441 papers. One author (JAUS) excluded 1333 of these as clearly irrelevant on the basis of title and abstract. A second author (FMW) independently reviewed a random selection of these and was in complete agreement. A further 71 papers were excluded after full text assessment by at least two authors (JAUS and FMW or MJT). The most common reasons for exclusion were that the papers included only a measure of the frequency of diabetic ketoacidosis and no further clinical details or it was not possible to separate the data for children with new onset diabetes (fig 1). We excluded three papers after contacting the authors as it was not possible to establish the definition of diabetic ketoacidosis used. A further eight papers were identified through citation searching. One paper compared the severity of type 1 diabetes at presentation in south east Sweden and Lithuania and so is reported as two studies.[18] The analysis is therefore based on 46 studies.

Study characteristics

The 46 eligible studies included more than 24 000 children in 31 different countries. Included studies showed considerable heterogeneity in terms of size, setting, length of study, and the proportion of children presenting in diabetic ketoacidosis (tables 1 and 2). Nearly three quarters of children (70%) were recruited from Canada (n=3947), Austria (n=3471), Finland (n=3002), Germany (n=2533), Sweden (n=2304), and the US (n=2181). Most studies included children from birth to 18 years old, but two included young adults up to the ages of 20 and 21 years.[19 20]

Studies used a wide range of definitions of diabetic ketoacidosis, but all included either pH values of ≤7.2 to <7.36 or bicarbonate values of <15 to ≤21 mmol/L. One study, which used two different definitions of diabetic ketoacidosis on the same cohort of children (pH <7.3 alone or combined with bicarbonate <15 mmol/L),[21] found an increased frequency of diabetic ketoacidosis when the definition based on pH alone was used (22.4%

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compared with 18.1%) but found no differences in the other conclusions based on definition used.

Study quality

All included studies were cohort studies and most recruited children retrospectively from hospital or clinic records. Study quality was variable, and formal assessment of ascertainment was performed in only 16 studies. We classified 12 studies as key papers (identified in table 1) and 28 as satisfactory. Only one study was excluded based on quality alone (see fig 1) as we were unable to adequately interpret the numerical data after contacting the author.

Analysis of identified factors

Together, the 46 studies compared 23 factors in children presenting with and without diabetic ketoacidosis. Table 3 shows these factors along with the number of studies and children included for each, and fig 2summarises the effect of these factors on the risk of presenting with diabetic ketoacidosis.

Individual factors

Age

Age was the most common factor described: 32 studies reported the effect of age on presentation, and 24 included data on the frequency of diabetic ketoacidosis in children grouped into different age ranges (fig 3).[8 19-41] Together, they showed that children <2 years old had three times the risk of presenting in diabetic ketoacidosis as children aged ≥2 years (odds ratio 3.41 (95% confidence interval 2.54 to 4.59), P<0.001, I^2=21.1%), and this association continued up to age 5 (odds ratio 1.59 (1.38 to 1.84), P<0.001, I^2=23.5%).

Four studies reported instead the mean age at diagnosis.[37 38 42 43] Combining these showed that children who presented with diabetic ketoacidosis tended to be younger than those without, but the difference was negligible (8.6 (SE 4.0) years *v* 8.7 (3.5) years, P=0.007). Data from the remaining six studies were insufficient for meta-analysis; four showed that younger children were more likely to present in diabetic ketoacidosis[44-47] while two reported no difference in mean[48] or median[49] age at diagnosis.

Sex

Twenty one studies reported the effect of sex on the frequency of diabetic ketoacidosis, of which 20 showed no effect and one (n=2121) reported a small but statistically significant increase in the frequency in girls (odds ratio 1.30 (1.07 to 1.58), P=0.0079).[25] Twelve studies compared the proportion of each gender presenting with and without diabetic ketoacidosis, and together gave a pooled odds ratio for boys of 0.93 (0.76 to 1.14, P=0.472, I^2=51.8%).[18] (fig 4).[21 25 26 35 36 40 50-53] Of the remaining nine studies, eight lacked sufficient data for meta-analysis[20 24 41 42 46-48 54] and one was a multivariate analysis of 262 children—which showed that, although female sex was significantly associated with increased risk of delayed diagnosis (symptomatic period ≥4 weeks) (odds ratio 2.78 (1.09 to 7.14), P=0.033), it was not associated with an increased risk of severe diabetic ketoacidosis (odds ratio 0.68 (0.26 to 1.83), P=0.450).[27]

Ethnicity

Seven studies explored the effects of ethnicity. Because of the heterogeneity of the populations, it was not possible to establish whether the frequency of diabetic ketoacidosis was significantly different in any particular race or ethnic group. However, five studies compared the frequency of diabetic ketoacidosis between two different ethnic groups. All showed a significant difference in the frequency of diabetic ketoacidosis, and in each case the ethnic minority group experienced an increased risk of diabetic ketoacidosis—in the US, non-Hispanic white people *v* others (odds ratio 0.55 (0.32 to 0.96)),[36] white people *v* Hispanic (odds ratio 0.33 (0.14 to 0.76)),[55] and non-Hispanic white *v* Hispanic (odds ratio 0.58 (0.37 to 0.89))[56]; and in the UK, white *v* others (odds ratio 0.39 (0.15 to 0.98))[57] and non-Asian *v* Asian (odds ratio 0.35 (0.18 to 0.66)).[22] A French study also reported that parental birth in France had no significant effect on the frequency of diabetic ketoacidosis,[43] and a Kuwaiti study showed no difference between Kuwaiti nationals, Arabs, Asians, and those with no identified citizenship.[47]

Family history of diabetes

Six studies reported the effect of family history of diabetes on presentation with diabetic ketoacidosis, of which five examined the influence of having a relative with diabetes at the time of diagnosis. Although having a first degree relative with type 1 diabetes decreased the frequency of diabetic ketoacidosis in three studies (odds ratios 0.60 (0.44 to 0.82)[58] and 0.15 (0.05 to 0.41)[47] (not combined as I^2=84.7%) and P<0.01[20]), it did not predict a diagnosis of new onset diabetes before progression to diabetic ketoacidosis in a US study after adjustment for age, sex, whether children were diagnosed in primary or secondary care, and duration of symptoms.[44] A German study which adjusted for age, sex, having a single parent, and social status also failed to show a significant association with a family history of either type 1 or type 2 diabetes in siblings, parents, or grandparents (odds ratio for positive family history *v* no family history 0.58 (0.20 to 1.66), P=0.312).[27]

Two studies examined the effect of being the first or second affected member of a family, thereby separating the effect of having an increased genetic risk of developing diabetes from the environmental effects of having a family member with diabetes at the time of diagnosis. Among Finnish children followed for a median of 7.7 years after initial diagnosis, those with a first degree relative with diabetes at the time of diagnosis had a significantly lower frequency of diabetic ketoacidosis than those in whom a family member was subsequently diagnosed with diabetes during the follow-up period (4.9% (4/90) *v* 21.4% (7/30), P<0.05; odds ratio 0.16 (0.04 to 0.59)). However, there was no difference between children in whom a family member was subsequently diagnosed with diabetes during the follow-up period and those without a family history at the end of the follow-up period (odds ratio 0.93 (0.39 to 2.20)).[58] A small UK study also showed that children who were the second affected child in a family were less likely to present in diabetic ketoacidosis than first affected children (odds ratio for second *v* first affected 0.07 (0.003 to 1.51), n=79).[48]

Body mass index

Two studies reported on the association between body mass index and a diagnosis of diabetic ketoacidosis and both showed a higher frequency of diabetic ketoacidosis in those children with a lower body mass index.[41 53]

Parental consanguinity

Two small studies from Saudi Arabia with parental consanguinity rates of >40% (19/40 and 47/110) failed to show a significant difference in the rate of diabetic ketoacidosis in children of consanguineous parents (combined odds ratio 1.19 (0.59 to 2.37), P=0.63, I^2=0).[28 29]

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Family factors

Parental education

Three studies reported on the influence of parental education. Having a mother with higher than secondary education was protective against developing diabetic ketoacidosis in Lithuania (odds ratio 0.4 (0.20 to 0.79)),[18] and in Finland children from families in which at least one parent had an academic degree had a lower incidence of diabetic ketoacidosis at presentation than those without (16.9% (43/254) *v* 24.4% (105/431), P<0.05, odds ratio 0.64 (0.43 to 0.94)).[34] The third study, set in Germany, did not report the effect of parental education on the presence or absence of diabetic ketoacidosis at presentation, but multivariate analysis showed that children from families in which parents had ≤9 years of education had a significantly increased risk of severe diabetic ketoacidosis (pH≤7.2) (odds ratio 3.54 (1.10 to 11.35), P for trend=0.034) compared with children whose parents had ≥12 years of education, even after adjustment for rates of delayed diagnosis.[27]

Family structure

Three studies explored the effects of family structure and found that neither living in a single parent family[48 27] nor the number of children in the family[43] were significantly associated with diabetic ketoacidosis at diagnosis (odds ratio 1.85 (0.43 to 7.82), P=0.411[27]).

Health insurance status

Three studies examined the influence of insurance status. Two US studies reported that lack of private insurance was a risk factor for presenting in diabetic ketoacidosis, with significantly more patients with either Medicaid or no insurance presenting in diabetic ketoacidosis (62% (13/21) and 48% (40/83) compared with 34% (40/118) and 22.5% (62/276) respectively, combined odds ratio 3.20 (2.03 to 5.04), P<0.001, I^2=0).[36 37] Children with no insurance also had a greater risk of presenting in diabetic ketoacidosis compared with those receiving Medicaid (odds ratio 2.84 (1.16 to 6.93)), but there was no difference between those with private insurance and those receiving Medicaid (odds ratio 0.54 (0.26 to 1.10)).[36] In contrast, a French study showed that the presence or absence of free medical assistance (aide medicale gratuite) was not significantly associated with diabetic ketoacidosis at diagnosis of diabetes.[43]

Rural or urban residence

Three studies found that living in rural or urban areas had no significant effect on rates of diabetic ketoacidosis at diagnosis. In Finland there was no difference in frequency of diabetic ketoacidosis between families living in a city, town, or suburb compared with those living in a village or rural areas,[34] while in Sweden and Lithuania the rates of diabetic ketoacidosis were not significantly different in those living in cities or small towns compared with those in villages (odds ratios 2.06 (0.80 to 5.30) and 0.63 (0.32 to 1.27) respectively).[18]

Family income, parental employment, and social status

Three studies examined the effect of family income. Two European studies found that family income had no significant effect on risk of presenting in diabetic ketoacidosis.[34 43] In contrast, a Canadian study, which adjusted for age and sex, showed that being from a family in the two lowest quintiles of family income was associated with an increased risk of diabetic ketoacidosis (odds ratio 1.38 (1.17 to 1.63)).[46]

Two studies examined the effect of parental employment on the frequency of diabetic ketoacidosis: in Sweden having a mother who did not work significantly increased the risk of presenting in diabetic ketoacidosis (odds ratio 4.8 (1.8 to 13.1)), whilst in Lithuania the father's employment status had no effect on the rate of diabetic ketoacidosis (odds ratio 1.17 (0.53 to 2.57)).[18] Only one study from the UK assessed the influence of social status. It did not provide numerical data, but reported that children with parents in social classes 3–5 were more likely to present in diabetic ketoacidosis than those in social classes 1 and 2 (P<0.05).[20]

Physician factors

Delayed diagnosis

Four studies explored the impact of delayed diagnosis (delay >24 hours for any reason) on the development of diabetic ketoacidosis. All reported that a significant proportion (16–51%) of children experienced a delay, but it was not possible to combine data because of different definitions of end points used. Delay of more than 24 hours between initial presentation to a primary or secondary care provider and referral to a multidisciplinary diabetes team in the UK was associated with an increased risk of presenting with diabetic ketoacidosis (52.3% *v* 20.5%, P<0.05, odds ratio 4.26 (1.54 to 11.79)).[57] A similar increase in risk occurred in children who were not diagnosed on the day of admission to a US children's hospital (59% (17/29) *v* 33% (35/105), P=0.0178, odds ratio 2.83 (1.22 to 6.58)).[37] In contrast, two European studies found no effect when there was a delay between the first medical consultation and hospitalisation (odds ratio 0.79 (0.31 to 2.00))[43] or delay of more than 24 hours between the first visit and diagnosis (odds ratio 0.98 (0.73 to 1.31)).[42]

Diagnostic error

Four studies in the US, France, and Poland looked specifically at the outcome of children in whom the diagnosis of type 1 diabetes was not made at the first medical consultation because of diagnostic error, judged to have occurred when children were not diagnosed on their first visit, either because they were given a misdiagnosis or signs and symptoms were missed or not recognised. Such children had a threefold increased risk of presenting in diabetic ketoacidosis (combined odds ratio 3.35 (2.35 to 4.79), P<0.001, I^2=0%) (fig 5).[37 43 59 60] This risk was independent of the presence or absence of infection preceding diagnosis,[59] but diagnostic error was significantly more likely to occur in younger children: the mean age of children who presented with diabetic ketoacidosis was 5.4 (standard error 4.4) years when the diagnosis was missed compared with 8.8 (4.0) years when the diagnosis was not missed (P<0.001).[37]

Number of medical consultations before diagnosis

Two studies reported the number of medical consultations that occurred before the diagnosis of diabetes. A Canadian study found that 84% (207/247) of children had been seen in primary care before referral to secondary care: 66% (163/247) on the day of diagnosis, 14% (35/247) once, and 4% (10/247) at least twice before the date of diagnosis.[44] However, the number of visits did not differ between children with and without diabetic ketoacidosis (P=0.30).[44] A US study found that significantly more children who presented with diabetic ketoacidosis had one or more medical consultations in the week before diagnosis (38.8% (285/735) *v* 34.4% (1104/3212), P=0.026).[46]

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Delayed treatment and presence of structured diabetes team

One multicentre study across Europe showed that a delay of more than 24 hours between diagnosis and treatment was associated with a small increased risk of children developing diabetic ketoacidosis (odds ratio 1.74 (1.10 to 2.77)).[42] One Kuwaiti study compared the frequency of diabetic ketoacidosis in children diagnosed in hospitals with and without a structured diabetes team, and found that diabetic ketoacidosis was significantly more common in hospitals lacking a structured diabetes team (P<0.002).[47]

Disease factors

Duration of symptoms

Four studies compared the duration of symptoms in children presenting with and without diabetic ketoacidosis.[25 35 38 61] Although the mean duration of symptoms was similar in both groups, it was slightly shorter in those with diabetic ketoacidosis (16.5 (SE 6.2) days and 17.1 (6.0) days respectively, P<0.001). Two other studies found that children with diabetic ketoacidosis had a shorter duration of symptoms (P<0.005),[47] but the percentage of children with symptoms for less than two weeks did not differ between the groups (24.8% (108/436) and 24.2% (145/601) for those with and without diabetic ketoacidosis respectively, P=0.80).[42] After adjustment for age, sex, family history of type 1 diabetes, and whether children were diagnosed in primary or secondary care, the duration of classic symptoms (enuresis or nocturia, polyuria, polydipsia, change in appetite, weight loss, candidiasis, and fatigue) also did not predict a diagnosis of new onset diabetes before progression to diabetic ketoacidosis.[44]

Pattern and frequency of symptoms

The six studies which compared symptom pattern and frequency between children with and without diabetic ketoacidosis showed inconsistent findings. One found no difference in the frequency of any of the typical symptoms of diabetes (enuresis or nocturia, polyuria, or polydipsia),[44] whereas children with diabetic ketoacidosis presented more often with vomiting,[43 35 40] abdominal pain,[43 35] dyspnoea,[40] weakness,[35] anorexia,[35] and changes in mental status.[35] Two studies also showed that children with diabetic ketoacidosis had significantly greater weight loss than those without (4.84% (SD 3.87%) of body weight *v* 3.32% (3.53%), P<0.0001; and 3.35 (SD 2.07) kg *v* 1.45 (1.85) kg, P<0.005),[42 61] while a third study showed no difference (P=0.296).[40]

Preceding infection or febrile illness

Three studies included data on the effect of a preceding infection or febrile illness. In two, a history of infection or febrile illness was associated with an increased risk of diabetic ketoacidosis (odds ratios 6.50 (2.06 to 20.53) and 1.87 (1.05 to 3.33), not combined because I^2=72.2%).[33 40] In the third study febrile illness before the start of symptoms was more common in the groups with shorter duration of symptoms (<1 month), but it did not change the percentage with severe ketoacidosis.[62]

Other factors

Time of year

Two studies[25 26] looked at the effect of time of year on the frequency of diabetic ketoacidosis. Although the total number of cases was higher in winter than in summer, both found that the proportion of diabetic ketoacidosis cases remained stable (combined odds ratio 1.07 (0.89 to 1.28), P=0.49).

Background incidence of type 1 diabetes

Only one multicentre study reported specifically on the influence of the background incidence of type 1 diabetes on the frequency of diabetic ketoacidosis. Using data from 11 centres across Europe, it showed a significant inverse correlation between the proportion presenting with diabetic ketoacidosis and the background incidence of type 1 diabetes for these centres (r_s=–0.715, P=0.012).[42]

Discussion

Principal findings

This systematic review provides a comprehensive synthesis of the factors associated with diabetic ketoacidosis in children and young adults presenting with new onset of type 1 diabetes. We found that younger children, those from ethnic minority groups, without medical insurance (in the US), and with a lower body mass index were at highest risk. Having a preceding infection and being exposed to diagnostic error or delayed treatment were also associated with an increased risk of developing diabetic ketoacidosis. In contrast, we found that children with a first degree relative with type 1 diabetes, with parents with higher levels of education, or who lived in an area with a higher background incidence of type 1 diabetes seemed less likely to present in diabetic ketoacidosis (see fig 2).

Strengths and limitations

Our rigorous and systematic search encompassed multiple databases and languages, and identified data on more than 24 000 children from 31 countries. Although this strengthens the generalisability of our findings, it also contributed to considerable heterogeneity in terms of design, setting, and predictors included. Despite using appropriate meta-analytic techniques with random effect models, we were unable to control fully for these differences. The studies also varied in quality, and only 18 formally assessed case ascertainment. Many were also retrospective and may have been subject to recording and recall bias. Most of the studies did not provide quantitative data for negative findings, but merely stated that no differences were observed, implying some degree of reporting bias. Although we cannot exclude publication bias, we expect this to be minimal because of the exploratory nature of the question.

Included studies also used a wide range of definitions of diabetic ketoacidosis, reflecting different international settings and periods of study. Only one[47] used the current diagnostic criteria for diabetic ketoacidosis published by the International Society for Paediatric and Adolescent Diabetes.[4] However, our inclusion criteria incorporated a measurement of pH (pH ≤7.2 to <7.36) or bicarbonate (<15 to ≤21 mmol/L) and so consistently identified those with worse metabolic derangements. Although the absolute frequency of diabetic ketoacidosis may vary with different definitions, it is unlikely that this would substantially alter our overall conclusions.[21] Finally, because of the format of the data, it was not possible to assess the independent contribution of each of the predictors we identified, but we include results of multivariate analyses where reported.

Factors associated with increased risk of diabetic ketoacidosis

Younger age was consistently associated with an increased risk of diabetic ketoacidosis at diagnosis. This increased risk was

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most noticeable in children less than 2 years old and was still present at 5 years, but by age 10 there was no significant difference. The reasons for this are probably multifactorial. Clinicians may have a lower index of suspicion for diabetes among younger children, and the classic symptoms of diabetes may be subtle and difficult to distinguish from other acute illnesses at this age. Decompensation due to dehydration and acidosis also develop more quickly in young children as the mechanisms of metabolic compensation are less developed.[29 38] Moreover, β cell destruction may be more aggressive in young children: serum levels of proinsulin C peptide are lower in children under 2 years old at diagnosis of diabetes, and they continue to lose their endogenous insulin secretory capacity faster than older children after diagnosis.[24 63] Some of these factors may also explain why children with a lower body mass index seemed to be at greater risk.

Children from ethnic minority groups seem to have an increased risk of developing diabetic ketoacidosis, but it is difficult to draw strong conclusions as the studies compared different ethnic groups, and we do not know the independent effect of ethnicity (rather than sociodemographic differences). Possible explanations include difficulties in recognising the symptoms because of language and cultural barriers, lack of awareness of type 1 diabetes in ethnic minorities, and cultural or practical difficulties in accessing healthcare.[64 65] These factors are also likely to contribute to the threefold increase in diabetic ketoacidosis seen in children without private health insurance in the US.

Several physician level factors were also associated with an increased risk of diabetic ketoacidosis. Children who were not diagnosed at their first visit to a doctor had a threefold increased risk of presenting in diabetic ketoacidosis, and delays in starting treatment were associated with a small increased risk. However, the contribution of delayed recognition itself was not consistent as some studies found delays contributed to diabetic ketoacidosis while others did not. The duration of symptoms was also similar in children with and without diabetic ketoacidosis, although this effect may be confounded by the age of children—as diabetic ketoacidosis is more common in younger children, who tend to have a shorter duration of symptoms.[10]

A history of prior infection was the only disease related factor associated with an increased risk of diabetic ketoacidosis. Infection is known to cause inflammation, pro-inflammatory cytokine release, and a counter regulatory response that collectively lead to insulin resistance and metabolic decompensation.[66] The infection itself may also trigger more rapid autoimmune destruction of β cells. Infections are associated with a transient increase in risk of type 1 diabetes,[67] and there is increasing evidence for the role of enteroviruses in the early phase of type 1 diabetes through infection of β cells and activation of innate immunity and inflammation.[68 69] Alternatively, the presence of infection may mask the early symptoms of diabetes and make the diagnosis more difficult.

Factors associated with a decreased risk of diabetic ketoacidosis

Having a first degree relative with diabetes was associated with an up to sixfold decreased risk of diabetic ketoacidosis at diagnosis. The absence of any significant difference between children in whom a member of the family was subsequently diagnosed with diabetes and those without such a family history at the end of the follow-up period suggests that the protective effect of a first degree relative with diabetes at diagnosis was probably due to increased awareness among families with experience of diabetes rather than an increased genetic risk for type 1 diabetes predisposing to a milder onset of disease, as suggested previously.[70] This interpretation is consistent with other observations that initial differences in metabolic indices observed at diagnosis between those with and without a family history of diabetes disappear by one year after diagnosis.[71]

It is also possible that some of this protective effect could be due to a family history of diabetes alerting clinicians to an increased possibility of type 1 diabetes. Better disease recognition because of improved awareness of diabetes is further supported by the finding that children from families with higher parental education were less likely to present in diabetic ketoacidosis, and that the risk of diabetic ketoacidosis was inversely proportional to background incidence of type 1 diabetes. These differences may also reflect variations in, for example, access to healthcare, child supervision, or schooling.

Implications for practising clinicians

This study has implications for clinicians in both primary and secondary care, as the vast majority of children who develop type 1 diabetes will have a consultation before diagnosis. Although type 1 diabetes can be diagnosed in primary care, a diagnosis of diabetic ketoacidosis requires measurement of serum pH or bicarbonate and so typically requires referral to secondary care. Furthermore, many children present directly to hospital emergency or paediatric departments. As with other serious illnesses in children, differentiating the occasional child with a serious illness from the large number with minor undifferentiated illness is challenging. The relatively easy access to point of care tests for hyperglycaemia, ketonaemia, and glycosuria, however, means that diagnosis does not require access to specialist diagnostic services (such as imaging for suspected malignancy) but, instead, a high index of suspicion. Our findings suggest that clinicians should be particularly alert for diabetic ketoacidosis in children under 5 years old, those from ethnic minority groups, and those from families with low education level or socioeconomic status.

We found clear evidence that at least some children with diabetic ketoacidosis experienced diagnostic or treatment delays. Children presenting with diabetic ketoacidosis had symptoms for a mean of two weeks, up to a third had at least one medical consultation in the week before diagnosis, and misdiagnosis was associated with a threefold increase in diabetic ketoacidosis. However, the influence of delays at the physician level on risk of diabetic ketoacidosis was not consistent across studies, and we did not identify reasons for the diagnostic errors. High rates of misdiagnosis have also been found in children presenting with type 1 diabetes without diabetic ketoacidosis, with up to 86% of children not diagnosed at first encounter.[37 43 59 72 73] In these studies, common diagnostic errors included misinterpreting symptoms (such as polyuria misdiagnosed as urinary tract infection), exclusively focusing on one or more symptoms (such as oral candidiasis), and not performing appropriate investigations (such as blood glucose or urine tests). Clinicians should therefore be aware of these difficulties in diagnosis and be particularly alert for diabetic ketoacidosis in those children at higher risk. Improving awareness among parents and clinicians about the early symptoms of diabetes through diabetes education programmes—such as the community intervention in Italy, which reduced the prevalence of diabetic ketoacidosis at diagnosis from 78% to 12.5%[74]—could also decrease the frequency of diabetic ketoacidosis.

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Implications for future research

While it seems intuitive that an earlier diagnosis of diabetes should lead to a decreased risk of diabetic ketoacidosis, our review still leaves unanswered the major question of whether diabetic ketoacidosis is a consequence of delayed diagnosis and treatment or whether it reflects a more aggressive form of diabetes.[10] Additionally, no studies addressed the reasons for delays in diagnosis or the relative contribution of individual, parental or physician factors. Further studies should explore the factors that influence help seeking behaviour among parents, and delineate the time course of clinical presentation of this disease. A better understanding of the patient pathway from symptom onset to diagnosis is needed to appropriately target interventions to decrease the frequency of diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults.

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Contributors: JAUS performed the literature search, selected articles for inclusion, extracted the data, performed the analysis, and wrote the first draft of the manuscript. FMW and MJT selected articles for inclusion, extracted the data, and reviewed and edited the manuscript. SJS assisted with the statistical analysis and reviewed and edited the manuscript.

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Data sharing: No additional data available.

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What is already known on this topic

A sizeable proportion of children and young adults with newly diagnosed type 1 diabetes present in diabetic ketoacidosis, which carries a substantial risk of life threatening complications

It is unclear why some children present in diabetic ketoacidosis whereas others do not and whether the development of diabetic ketoacidosis is a consequence of delayed diagnosis and treatment

What this study adds

This systematic review of 46 studies including more than 24 000 children in 31 different countries provides the first synthesis of the factors associated with diabetic ketoacidosis at the onset of type 1 diabetes in children and young adults

Younger age, diagnostic error, ethnic minority status, lack of health insurance in the US, lower body mass index, preceding infection, and delayed treatment were all associated with an increased risk of diabetic ketoacidosis, while having a first degree relative with type 1 diabetes at the time of diagnosis, higher parental education, and higher background incidence of type 1 diabetes appear to be protective

The mean duration between onset of symptoms and development of diabetic ketoacidosis is over 14 days, and up to a third of children have at least one medical consultation during that period, suggesting a possible window of opportunity to improve recognition

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Tables

Table 1| Characteristics of 46 studies included in systematic review to identify factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

Study	Country	Period of study	No of study centres	Design*	Recruitment method
Abdul-Rasoul et al, 2010[47]†	Kuwait	2000–6	Nationwide	R	Hospital records
Al Khawari et al, 1997[30]	Kuwait	1992–5	Nationwide	P	Kuwait IDDM register; Hospital records; Diabetic clinic mandatory registry
Alvi et al, 2001[22]	UK	1987–96	Regional	R	Local paediatricians; General practitioners and diabetes nurse specialists
Blanc et al, 2003[43]†	France	Not given	1 Endocrinology and diabetes department	P	Hospital records
Bober et al, 2001[33]	Turkey	1991–8	1 Paediatric endocrinology department	R	Hospital records
Bowden et al, 2008[8]	USA	2004	1 Children's hospital	R	Hospital records
Bui et al, 2010[46]†	Canada	1994–2000	Regional	R	Health insurance plan; Database of health and long term care; Discharge abstract database
Charemska et al, 2003[23]	Poland	1998–2002	1 Children's hospital	R	Clinic records
Hekkala et al, 2007[21]	Finland	1982–2001	1 Paediatric department	R	Hospital and clinic register
Hekkala et al, 2010[53]	Finland	2002–5	27 Centres	R	Paediatric diabetes register; Hospital records
Hodgson et al, 2006[50]	Chile	1988–2003	1 Hospital	R	Hospital records
Kapellen et al, 2001[61]†	Germany	1995–9	1 Children's hospital	R	Hospital records
Komulainen et al, 1996[34]‡	Finland	1986–9	Nationwide	P	Diabetes nurses; National Central Drug Registry
Komulainen et al, 1999[24]†‡	Finland	1986–9	Nationwide	P	Diabetes nurses; National Central Drug Registry
Levy-Marchal et al, 2001[42]†	Europe	1989–94	24 EURODIAB centres	R	Incidence surveillance cohort
Mallare et al, 2003[37]†	USA	1995–8	1 Children's hospital	R	Hospital records
Maniatis et al, 2005[36]	USA	2002–3	1 Diabetes centre	R	Diabetes centre records
Mayer-Davies et al, 2009[19]	USA	2002–5	6 Clinical centres	P	Reporting network of clinics and healthcare providers; Hospital discharge, billing, and paediatric endocrinology case lists; Mailed survey to providers likely to see children not included in above
Mlynarski et al, 2003[49]	Poland	1997–2001	1 Diabetes centre	P	Hospital records
Neu et al, 2003[25]†	Germany	1987–97	31 Paediatric departments, 1 diabetes centre	R	Hospital records; Questionnaire to members of Diabetic Patients Association
Newfield et al, 2009[55]	USA	1998–2001	1 Children's hospital	R	Hospital database
Olak-Bialori et al, 2007[26]	Poland	2004–5	1 Children's endocrinology and diabetes centre	R	Clinic records
Pawlowicz et al, 2008[59]§	Poland	1999–2004	1 Paediatric endocrinology department	R	Hospital records; Regional diabetic polyclinic records
Pawlowicz et al, 2009[60]†§	Poland	1999–2005	1 Paediatric endocrinology department	R	Hospital records; Regional diabetic outpatient clinics
Pinkney et al, 1994[20]	UK	1990 1985–6	Regional	P	Prospective registration; Hospital discharge records and death certificates; General practitioners
Pocecco et al 1993[39]	Italy	1987–90	14 Paediatric departments, 14 diabetes services	R	Departmental records; Central register for all patients receiving drug reimbursement
Prisco et al, 2006[51]	Italy	2003	7 Territorial reference hospitals	P	Hospital records
Quinn et al, 2006[44]†	USA	1990–9	1 Children's hospital	R	Hospital records
Roche et al, 2005[45]	Ireland	1997–8	Nationwide	P	Irish paediatric surveillance unit; National survey of adult physicians and endocrinologists

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Table 1 (continued)

Study	Country	Period of study	No of study centres	Design*	Recruitment method
Rosenbauer et al, 2002[27]	Germany	1993–5	41 Paediatric and diabetes departments	R	Active clinic based surveillance system; Yearly surveillance among paediatric, general, and internal medicine practices
Salman et al, 1991[29]§	Saudi Arabia	1985–9	1 Children's hospital	R	Hospital records
Salman et al, 1991[29]§	Saudi Arabia	1985–9	1 Children's hospital	R	Hospital records
Samuelsson et al, 2005[38]	Sweden	1977–2001	7 Paediatric clinics	R	Medical records; Swedish Diabetes Register
Saudaskaite-Kuehne et al, 2002[15]†	Sweden	1995–9	12 Hospitals	P	Existing case-control study
Saudaskaite-Kuehne et al, 2002[18]†	Lithuania	1996–2000	Nationwide	P	Existing case-control study
Savova et al, 1996[62]	Bulgaria	1974–96	1 Children's hospital	R	Hospital records; National centralised system of insulin delivery
†Schober et al, 2010[41]	Austria	1989–2008	Nationwide	P	Network covering all paediatric hospitals, wards, and diabetologists
Sebastiani et al, 1992[31]¶	Italy	1989–90	51 Local health units, 71 hospitals	P	Basic incidence surveillance cohort
Smith et al, 1998[48]	UK	1990–6	1 Children's hospital	R	Clinic records
Soliman et al, 1997[32]	Oman	1990–3	Regional (10 hospitals)	P	Diabetologists and pediatricians in regions
Sundaram et al, 2009[57]†	UK	2004–7	1 Children's hospital	R	Hospital database
Tahirovic et al, 2007[54]	Boznia and Herzegovina	1990–2005	1 Children's hospital	R	Prospective local diabetes register; Hospital records
Ting et al, 2007[35]	Taiwan	1979–2006	1 Paediatric department	R	Hospital records
Vehik et al, 2009[56]†	USA	2002–4	Regional	R	Search for Diabetes in Youth Study (rapid reporting network of clinics and healthcare providers)
Veijola et al, 1996[58]‡	Finland	1986–9	Nationwide	P	Diabetes nurses; National Central Drug Registry
Xin et al, 2010[40]	China	2004–8	1 Hospital	R	Hospital records

*R=Retrospective; P=Prospective.

†Papers assessed as key papers through quality assessment.

‡Papers probably based on the same cohort of children, but not possible to combine the results as the later study (Komulainen et al,1999[24]) included only those children with blood pH, c peptide, and HbA_{1c} measurements, whereas earlier papers (Komulainen et al, 1996[34] and Veijola et al, 1996[58]) report on different data. The three papers are therefore reported as separate studies, but the children included only once in the total number of children studied.

§Probably overlap in the subjects reported in these papers as the children were recruited from the same hospitals over the same time, but, because the numbers differed in the two papers, it was not possible to combine the data.

¶This paper reports on the EURODIAB experience in Lazio. Although Lazio is also included in the combined report of the EURODIAB study (Levy-Marchal et al, 2001[42]), the numbers of subjects and focus of analysis are different and so this report is treated as a separate study.

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Table 2| Characteristics of subjects in 46 studies included in systematic review to identify factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

				Diabetic ketoacidosis		
Study	Sample size	Age (years)	Male (%)	Definition(s)	Ascertainment (%)	Prevalence (%)
Abdul-Rasoul et al, 2010[47]	677	0–<12	47.4	pH <7.3 or HCO_3 <15 mmol/L, with ketonuria and glucose >11 mmol/L	93.9	37.7
Al Khawari et al, 1997[30]	243	0–<15	53.1	pH <7.3 or HCO_3 <18 mmol/L, with hyperglycaemia and ketonuria	92	49
Alvi et al, 2001[22]	328	0–15	55	pH ≤7.25 or HCO_3 ≤15 mmol/L, with hyperglycaemia and ketonuria		27
Blanc et al, 2003[43]	72	0–<18	50	pH <7.35		54
Bober et al, 2001[33]	62	0–<18	48.4	pH <7.3 and HCO_3 <15 mmol/L		29
Bowden et al, 2008[8]	152	0–?		HCO_3 <15 mmol/L, ketonuria, and hyperglycaemia		32.9
Bui et al, 2010[46]	3947	0–<18		Diagnostic codes 250.1–250.3		18.6
Charemska et al, 2003[23]	158	0–<19		pH ≤7.3 and HCO_3 ≤18 mmol/L		38
Hekkala et al, 2007[21]	585	0–<15	56.1	pH <7.3 or HCO_3 <15 mmol/L		22.4
Hekkala et al, 2010[53]	1616	0–<15	56.5	pH <7.3	97.6	19.4
Hodgson et al, 2006[50]	97	0–<17	63	pH <7.3, HCO_3 <15 mmol/L, and ketonaemia		37
Kapellen et al, 2001[61]	104	0–<18	55.8	pH <7.3, glucose >250 mg/dL, and HCO_3 <15 mmol/L		29.8
Komulainen et al, 1996[34]	801	0–<15	54.9	pH <7.3	100	
Komulainen et al, 1999[24]	745	0–<15	55.3	pH <7.3	93	21.6
Levy-Marchal et al, 2001[42]	1037	0–<15		pH <7.3	91	42
Mallare et al, 2003[37]	139	0–<19	52.2	pH <7.3	81.3	38
Maniatis et al, 2005[36]	359	0–<18	57.7	pH <7.3 and HCO_3 <15 mmol/L	93.7	28.4
Mayer-Davies et al, 2009[19]	436	0–<20		pH <7.25 (venous) or <7.3 (arterial/capillary), HCO_3 <15 mmol/L, code 250.1 at discharge, or diabetic ketoacidosis in medical notes		25.2
Mlynarski et al, 2003[49]	106	0–<19	62.3	pH <7.35		54.7
Neu et al, 2003[25]	2121	0–<15		Glucose >250 mg/dL, pH <7.3, or HCO_3 <15 mmol/L, with ketonuria	97.2	26.3
Newfield et al, 2009[55]	136	0–<18	55.9	pH <7.3 or HCO_3 <15 mmol/L		27.2
Olak-Bialori et al, 2007[26]	186	0–<18	53.8	pH <7.3, HCO_3 <18 mmol/L, ketonuria, and glucose 250mg/dL		33
Pawlowicz et al, 2008[59]	335	0–<17	51.94	pH <7.35 and HCO_3 <19 mmol/L	91.85	39.7
Pawlowicz et al, 2009[60]	474	0–<17	51.3	pH <7.3 and HCO_3 <15 mmol/L	99.73	32.9
Pinkney et al, 1994[20]	95	0–<21	56.5	pH ≤7.35 or HCO_3 ≤21.0 mmol/L	—	26
	219		59.8		>95	25
Pococco et al 1993[39]	73	0–<17	64.4	pH <7.36	98	41.1
Prisco et al, 2006[51]	118	0–<19	53.4	pH <7.3, glucose >250 mg/dL, and capillary ketone bodies >3 mmol/L	98	32.2
Quinn et al, 2006[44]	247	0–<6	59	Glucose >300 mg/dL, pH <7.3 or HCO_3 or tCO_2 <15 mmol/L		43.7
Roche et al, 2005[45]	197	0–<15	51.2	Glucose >15 mmol/L, urinary ketones +2, pH <7.2, HCO_3 <15 mmol/L, and clinical symptoms	90.7	25
Rosenbauer et al, 2002[27]	262	0–<15	53.4	pH ≤7.35	92.5	53.8
Salman et al, 1991[28]	110	0–<13	46.3	HCO_3 <15 mmol/L, glucose >15 mmol/L, ketonuria, and clinical features		67.3
Salman et al, 1991[29]	41	0–<5	53.7	HCO_3 <15 mmol/L, glucose >15 mmol/L, ketonuria, and clinical features		68.2
Samuelsson et al, 2005[38]	1903	0–<16	54.1	pH ≤7.3	100 (but 78.5 for pH)	12.8
Saudaskaite-Kuehne et al, 2002[15]	401	0–<16	51.1	pH ≤7.2 plus hyperglycaemia and ketonuria	83.4 South east Sweden, 49.5 Skane region	14.5

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Table 2 (continued)

Study	Sample size	Age (years)	Male (%)	Diabetic ketoacidosis		
				Definition(s)	Ascertainment (%)	Prevalence (%)
Saudaskaite-Kuehne et al, 2002[18]	286	0–<16	46.5	pH ≤7.2 plus hyperglycaemia and ketonuria	100	34.6
Savova et al, 1996[62]	1248	0–<18	49.4	pH <7.34 or acidotic breathing		35.3
Schober et al, 2010[41]	3331	0–15	53.9	pH <7.3	>93	37.2
Sebastiani et al 1992[31]	117	0–<15	44	pH <7.3		35.65
Smith et al, 1998[48]	79	0–<16	58.2	pH <7.3 or HCO_3 <18 mmol/L	90	27
Soliman et al, 1997[32]	60	0–<15		pH <7.35		41.7
Sundaram et al, 2009[57]	99	0–<16	55	pH <7.3 or HCO_3 <15 mmol/L with blood glucose >11 mmol/L and ketonaemia (with or without ketonuria)		27.2
Tahirovic et al, 2007[54]	100	0–≤14		pH <7.3 and HCO_3 <15 mmol/L	91.7	48
Ting et al, 2007[35]	304	0–<18	48	Glucose >200 mg/dL, pH <7.3 or HCO_3 <15 mmol/L, and ketonuria		65
Vehik et al, 2009[56]	712	2–<18	53	pH <7.3, HCO_3 <18 mmol/L, or physician diagnosed episode of diabetic ketoacidosis at diagnosis	75–76	27
Veijola et al, 1996[58]	801	0–<15	54.9	pH <7.3	100	21.7
Xin et al, 2010[40]	203	0–<15	43.3	pH <7.3 or HCO_3 <15 mmol/L, with glucose >14 mmol/L in presence of ketonuria		41.9

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Table 3| **Identified factors associated with diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults in systematic review of 46 studies**

		No of children	
	No of contributing studies	Total	No (%) with diabetic ketoacidosis
Individual patient factors			
Age	32	18 000	5273 (29)
Sex	21	16 969	4875 (29)
Ethnicity	7	2 383	741 (31)
Family history of type 1 diabetes	6	2 475	803 (32)
Body mass index	2	4 947	1551 (31)
Parental consanguinuity	2	151	102 (68)
Family factors			
Parental education	3	1 694	459 (27)
Family structure	3	413	201 (49)
Health insurance status	3	570	162 28)
Rural or urban residence	3	1 432	318 (22)
Family income	3	4 764	935 (20)
Parental employment	2	687	157 (23)
Social status	1	314	80 (25)
Physician factors			
Delayed diagnosis	4	1 347	555 (41)
Diagnostic error	4	1 020	381 (37)
No of medical consultations before diagnosis	2	4 450	892 (20)
Delayed treatment	1	1 037	436 (42)
Presence of structured diabetes team	1	677	255 (38)
Disease factors			
Duration of symptoms	7	6 393	1828 (29)
Pattern and frequency of symptoms	6	3 106	1308 (42)
Preceding infection or febrile illness	3	1 513	544 (36)
Other			
Time of year	2	2 307	619 (27)
Background incidence of type 1 diabetes	1	1 037	436 (42)

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Figures

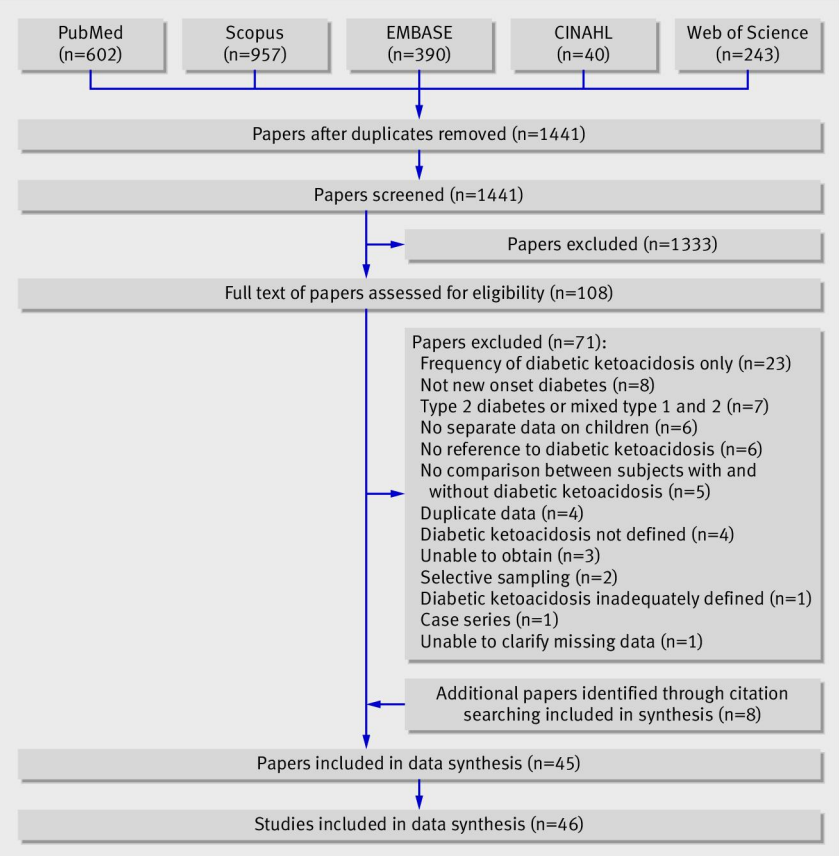

Fig 1 Selection of studies used in review

	Risk of diabetic ketoacidosis		
	Factors increasing risk	**Factors not affecting risk**	**Factors reducing risk**
More studies, greater consensus ↓ Fewer studies, weaker consensus	Younger age Diagnostic error Ethnic minority status Lack of health insurance (in US) Lower body mass index Preceding infection Delayed treatment Lower socioeconomic status Unemployed mother	Sex Duration of symptoms Rural or urban residence Family structure Time of year Family income No of medical consultations before diagnosis Parental consanguinuity Lack of medical insurance (in France) Father's employment status	Family history of type 1 diabetes Higher parental education Higher background incidence of type 1 diabetes Presence of structured diabetes team
Insufficient evidence	◄---------- Pattern and frequency of symptoms Delayed diagnosis		----------►

Fig 2 Influence of individual, family, physician, and disease factors on risk of diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

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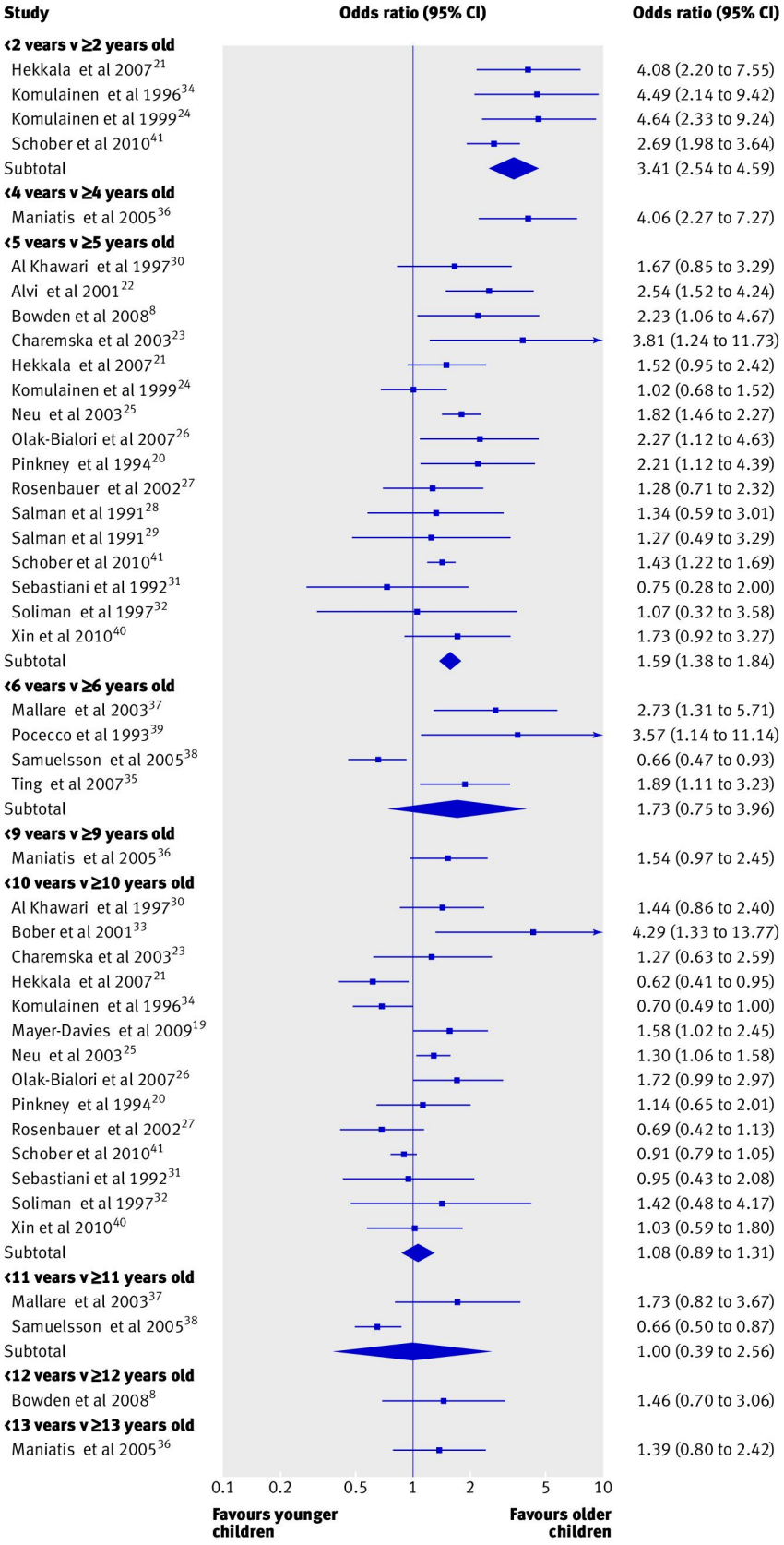

Fig 3 Forest plot showing the effect of different age cut-off points on the risk of presenting in diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

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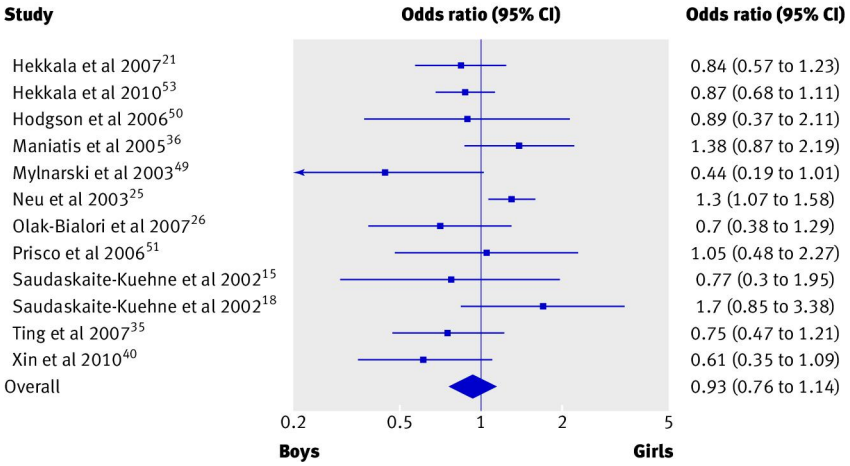

Fig 4 Forest plot showing the effect of sex on the risk of presenting in diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

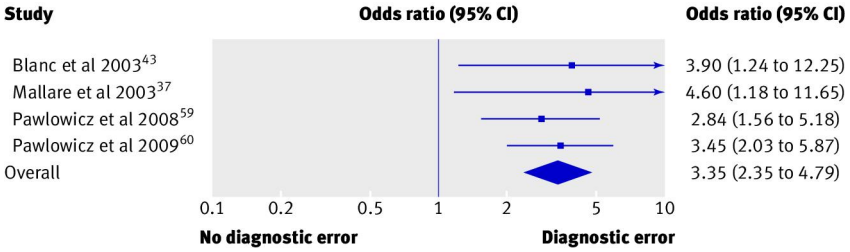

Fig 5 Forest plot showing the effect of diagnostic error on the risk of presenting in diabetic ketoacidosis at diagnosis of type 1 diabetes in children and young adults

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