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Have interventions aimed at assisting general practitioners in facilitating earlier diagnosis of type 1 diabetes in children been successful? A systematic review protocol

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ABSTRACT

Background Early diagnosis of type 1 diabetes in children is critical to prevent deterioration to diabetic ketoacidosis (DKA), a state where the body's insulin levels are critically low resulting in the use of fat for fuel and the accumulation of ketones. DKA is a life-threatening emergency where dehydration and cerebral oedema can quickly develop and lead to death. Despite treatment, DKA also has harmful impacts on cognition and brain development. Most children admitted to a hospital with DKA see their general practitioner in the week leading up to their admission. A delay in referral from general practice can result in delays in commencing lifesaving insulin therapy. Prior systematic reviews have explored publicity campaign interventions aimed at recognising type 1 diabetes earlier; however, no reviews have explored these interventions targeted at reducing the delay after presentation to the general practitioner. This systematic review aims to summarise interventions that target the diagnostic delay emerging from general practice and to evaluate their effectiveness in reducing DKA admissions.

Methods Six databases (Ovid (MEDLINE), Web of Science, EMBASE, CINAHL, Evidence-Based Medicine Reviews (EBMR) and Google Scholar) will be searched to identify studies exploring interventions to reduce diagnostic delay in children with type 1 diabetes, and hence DKA, in general practice. The primary outcome will be the number of DKA admissions to a hospital following a delay in general practice. The secondary outcome will be the behaviour of general practitioners with respect to urgent referral of children with type 1 diabetes. Title, abstract and full-text screening for exclusion and inclusion of publications will be completed by two independent reviewers. Any risks of bias within individual studies will be assessed by two independent reviewers, using the Risk Of Bias In Non-Randomized Studies of Interventions tool. Our confidence in the overall body of evidence will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation.

Ethics and dissemination The systematic review will be disseminated via publication and potentially in conference presentations. Ethics is not required for a systematic review of secondary data.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review will address a gap in the current literature surrounding childhood diabetic ketoacidosis (DKA) prevention research by focusing solely on the diagnostic delay interval.
⇒ This systematic review is topical given the identification of reducing delays in diagnosis of type 1 diabetes from primary care as a key DKA prevention target.
⇒ This systematic protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ This review will focus on non-randomised studies of interventions and feasibility studies due to the nature of the research question, leading to the anticipated high heterogeneity of results and the potential for quantitative synthesis to be inappropriate.
⇒ This systematic review is limited to publications in English only, due to the capacity of the research team.

PROSPERO registration number CRD42023412504

INTRODUCTION

Early diagnosis of type 1 diabetes is critical

Early diagnosis of type 1 diabetes mellitus (T1DM) is critical to prevent deterioration to diabetic ketoacidosis (DKA).[1] DKA is a severe complication of diabetes where insulin levels are depleted below levels needed for the body to use glucose, leading to hyperglycaemia, metabolic acidosis and ketosis.[2] DKA is a life-threatening emergency, being the most common cause of death in children with T1DM.[3] A single episode of moderate to severe DKA in children at diagnosis of T1DM has lasting effects, being also associated with lower cognitive ability and altered brain development when compared with children who also have T1DM but no or mild DKA.[4] DKA

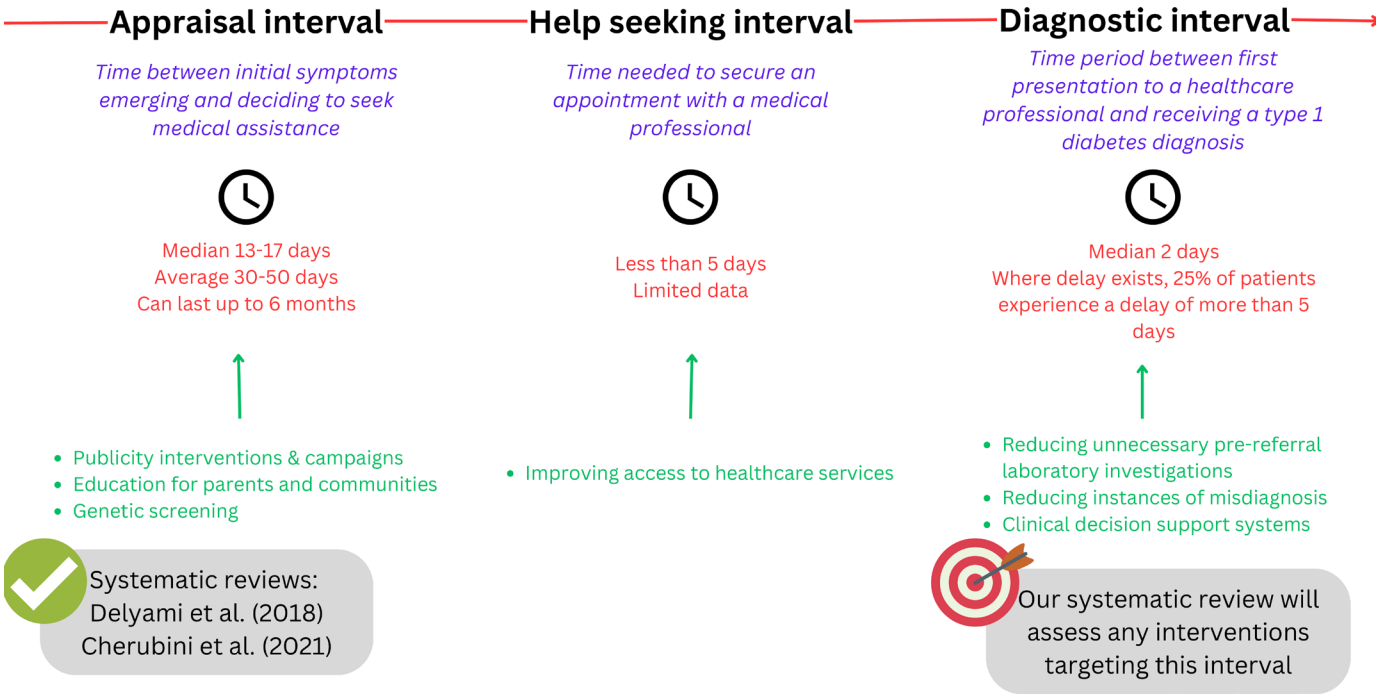

Figure 1 The pathway to a type 1 diabetes diagnosis in children.

at diagnosis of T1DM is entirely preventable provided timely diagnosis and initiation of insulin treatment.

The pathway to a type 1 diabetes diagnosis

Prior research has identified three distinct intervals (see figure 1) that constitute the pathway to receiving a T1DM diagnosis.[5] The first is the appraisal interval, which is defined as the time it takes between the onset of T1DM-related symptoms and the decision to seek help from a healthcare professional. The second is the help-seeking interval, defined as the time it takes to engage the services of a primary healthcare provider. The third interval is the diagnostic interval; this is the time it takes from the first presentation to a primary care professional to receive the diabetes diagnosis. DKA severity can progress rapidly; therefore, it is important that interventions are designed to shorten each of these intervals as much as possible.

Several publicity campaigns have targeted the first interval, the appraisal interval. These interventions aim to improve members of the public and health practitioners' awareness of the symptoms of T1DM, as well as the dangers of DKA. This includes poster campaigns, television and newspaper advertisements, letters to childcare centres and schools and online promotion campaigns through social networks.[6] Recent systematic reviews have demonstrated that these interventions have varying levels of success.[6 7]

To our knowledge, no systematic review has investigated the effectiveness of interventions that address the third interval, the diagnostic interval. Targeting this interval has the potential to greatly reduce DKA admissions, as the majority of children who present to a hospital in DKA are seen by a general practitioner (GP) leading up to their diagnosis.[1] 75%–80% of Australian children hospitalised with DKA see their GP in the week leading up to their admission.[8] As such, we will quantify the diagnostic delay interval as being a maximum of 7 days. The median diagnostic delay for Australian children is 2 days where a delay exists, and one-quarter of Australian children experience a delay of up to 5 days.[9] A delay of more than 24 hours between the initial presentation to a GP and a diagnosis has been associated with an increased risk of DKA presentation.[10] This is why timely confirmation of T1DM diagnoses with urgent referral to a paediatric team has been identified as a target DKA prevention strategy in another recent systematic review.[11 12]

The importance of this systematic review

Diagnosing T1DM in a timely manner is tremendously challenging. Symptoms of T1DM are non-specific and easily attributed to childhood development.[13] T1DM also occurs relatively infrequently in the population,[14] with GPs having to describe recognising the condition as 'looking for the needle in the haystack'.[5] The two most cited reasons for diagnostic delay are misdiagnosis and awaiting prereferral investigations such as laboratory blood tests to confirm diabetes before referral to a specialist team.[9 10 15–19] Implementation of interventions to assist GPs in reducing both instances of prereferral investigations and misdiagnosis could prevent up to a third of DKA admissions.[20]

The objective of this systematic review is to summarise interventions that reduce instances of misdiagnosis or prereferral investigations and to evaluate their effectiveness. The results of this study will form the basis for several interventions to assist GPs in facilitating earlier diagnosis for children.

METHODS AND ANALYSIS

This protocol has been registered through the PROSPERO database (CRD42023412504). This manuscript is being reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols statement. The checklist has been attached in online supplemental file 1.

Eligibility criteria

Study characteristics

There are limited data available in this research area,[6 7] and it is difficult to randomise intervention groups to answer this research question, as it involves prospective diagnoses and presentation to a hospital. Therefore, non-randomised studies of interventions (NRSIs) will be focused on in this review. This systematic review will define NRSIs as any quantitative investigation estimating the effectiveness of an intervention that does not use randomisation to allocate participants to control or intervention groups, in line with the Cochrane definition.[21] There is also an anticipated lack of studies which have designed interventions to target the diagnostic delay window of interest; therefore, feasibility studies with anecdotal evidence will also be included in the review.

Participants

This review will include interventions targeting the recognition of T1DM in paediatric patients. This will be defined as patients under 18 years of age, without a prerecorded diagnosis of diabetes. The group to which the interventions are targeted to is GPs; therefore, this review will be restricted to interventions that took place in the primary care setting.

Type of interventions

This review will be focused on studies involving interventions that are specifically aimed at reducing diagnostic delay for paediatric patients with T1DM in the primary care setting. Publicity interventions and campaigns will be excluded. Interventions in hospitals involving children who already have DKA will be excluded.

Outcome measures

Primary outcome measures

The number of children presenting to a hospital with DKA who had experienced a diagnostic delay following attendance at a general practice.

Secondary outcome measures

GPs' use of point of care tests in place of prereferral laboratory investigations, overall recognition of T1DM and other methods to facilitate referral to paediatric specialist teams.

Report characteristics

Studies completed within the last 20 years will be considered, ensuring relevance to the current general practice context. This review will be restricted to English language studies only, due to the language capacity of the systematic review team.

Table 1 Draft search command (Ovid)

#	Search command (MEDLINE)
1	Paediatric* or paediatric* or child* or adolescen* or youth or girl* or boy* or 'young people'
2	'type 1 diabetes' or t1d or T1DM or 'insulin dependent diabetes' or 'juvenile diabetes' or 'diabetes type 1' or 'diabetes mellitus type 1' or iddm or ((ketoacido* or dka) adj2 (present* or onset or diagnos*)) or ketoacidosis
3	Diabetes Mellitus, Type 1/di (Diagnosis) (MeSH)
4	Diabetic Ketoacidosis (MeSH)
5	((diagnos* or referral) adj2 (delay* or late or missed)) or present* or admission* or intervent* or opportunit* or reduc* or prevent* or communit*
6	'general practice' or 'primary care' or 'family medic*' or GP or 'general practitioner*' or 'primary care practitioner*' or 'primary care doctor*'
7	2 or 3 or 4
8	1 and 5 and 6 and 7

Information sources

The librarian at the University of Melbourne Faculty of Medicine, Dentistry and Health Sciences (VB) assisted the first author (CB) in creating and developing the search strategy.

The following electronic databases will be searched:

- Ovid (MEDLINE)
- EMBASE
- Web of Science platform
- CINAHL
- Evidence-Based Medicine Reviews (EBMR)
- Google Scholar

A draft search strategy for Ovid (MEDLINE) created for this project is provided in table 1. The search syntax will be tested and optimised in Ovid/MEDLINE and will be replicated in other databases with the syntax changed where required.

A grey literature search will also be conducted to identify any studies that are not in the electronic databases. Conference abstracts from the following organisations will be searched:

- International Society for Paediatric and Adolescent Diabetes
- Australian Paediatric Society
- American Diabetes Association
- European Association for the Study of Diabetes

If the corresponding full-text articles cannot be located in the conference abstracts, the authors of the abstracts will be contacted for further information. Authors of full-text publications may also be contacted for any further updates on their investigations or to clarify reported information. They may also be contacted to ascertain whether any key publications were missed when the final list of publications is formed.

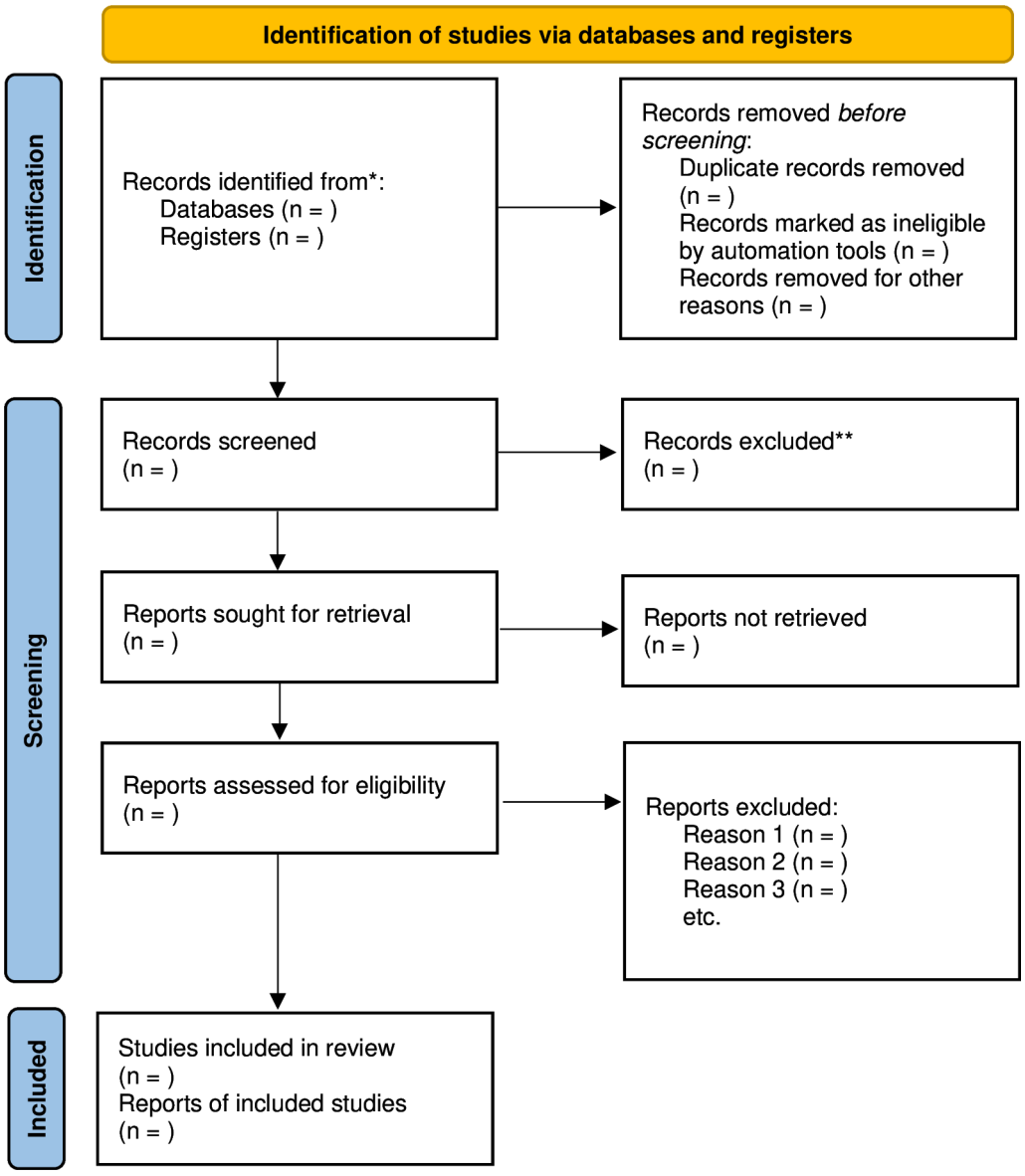

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols flow diagram.

We will also cross-check the reference lists of all publications selected for inclusion in this systematic review, as well as any other current, potentially relevant publications.

Screening and data management methods

Data management

Covidence[22] will be used to store and manage records and data throughout the review. This involves storing records generated by searching the databases, removing duplicate citations and storing any discarded references at each stage of the review.

A PRISMA[23] flow diagram will be used to document each stage of the review, and each individual search will be documented in the table following the format outlined in figure 2.

Screening and selection process

Two independent reviewers will be involved in the screening of titles and abstracts, to determine whether they should be included in the review. The decision will be based on the set eligibility criteria established above. The same independent reviewers will be involved in full-text screening to establish whether the publications accepted in the title and abstract review stage are to be included in the review. The number of publications included and excluded will be documented in a PRISMA[23] flow diagram, with any reason for exclusion noted. A table with justifications for the exclusion of each individual publication in the full-text review stage will also be included.

Data extraction methods

Two individuals will be involved in data extraction. Covidence[22] will be used to extract and document the data collection process in this review, in line with the Cochrane Handbook for Systematic Reviews of Interventions.[21] The information that will be recorded as follows:

- Initials of individual extracting the data and date of data extraction
- An assigned ID number to the publication agreed on by the individuals partaking in the extraction
- Study setting, region and year completed
- The type of study completed in the publication: observational cohort study, case-control study, feasibility study, etc
- Recruitment strategy and whether intervention was only applied to a cluster of general practice clinics
- Intervention type and length
- Definition of control groups/methods of comparison
- Outcome type: DKA presentations, children with reduced diagnostic delay time and GPs' behaviour
- Statistical analysis methods used
- Key results
- Key conclusions
- Whether any correspondence is required
- Potential conflicts of interest and sources of funding
- Miscellaneous

Whether correspondence is required to clarify reported data or to gain further information will be documented. Once the data extraction phase is completed, all publications that require correspondence with authors will be contacted, and information about the correspondence will be added under the miscellaneous section or under other relevant headings depending on the details of the correspondence.

If data are missing, authors of relevant publications will also be contacted to request the data. If the data cannot be provided to us, it will be reported as missing under the miscellaneous section. Any data that have been imputed will also be noted in the results section of the data extraction spreadsheet.

Outcomes and prioritisation

Data will be sought for interventions in general practice that aim to generate outcomes relating to reducing overall moderate or severe DKA admissions, whether children experience a diagnostic delay between presentation to the GP and receiving treatment for their diabetes or whether GP's behaviour in quickening referral of children to paediatric specialist teams has changed. Data for these specific outcomes will be sought after as they all represent methods of potentially reducing DKA admissions overall by shortening the diagnostic delay window. Publications involving interventions with GPs with aims to assess any of the outcomes listed will be included in this review.

Priority will be assigned to publications assessing the outcome of reduction in DKA admissions in children, as this is addressing the primary objective of introducing the interventions in general practice.

Risk of bias in individual studies

The Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool[24] will be used to assess any risk of bias in the individual studies. The tool aims to identify risks of bias in NRSIs, by assessing seven key bias domains. This includes the following:

At preintervention:

- Bias due to confounding
- Bias in the selection of participants into the study

At intervention:

- Bias in the classification of interventions

Postintervention:

- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in the selection of reported results

A separate spreadsheet will include the aforementioned bias areas where reviewers will use the ROBINS-I overall risk of judgement table[24] to classify each area as having low, moderate, serious or critical risk of bias. If there are no information available for the area of bias, this will be documented as 'no information' in these sections.

Any studies at critical risk of bias found in individual publications will be documented and removed from the final analysis when evaluating the individual studies. This is in line with Cochrane guidelines.[21] If there is any disagreement among the two reviewers at this stage, a third independent reviewer will be involved to discuss a possible resolution.

Data analysis

Due to the anticipated diversity of the NRSIs and feasibility studies included in this systematic review, a high level of heterogeneity is expected. As a result, should the studies be sufficiently similar enough to merit conduction of meta-analyses, a random-effects meta-analysis will be completed in Stata Copyright 1996–2023 StataCorp LLC.[25] The effect of the intervention will be estimated using risk ratios with standard errors with 95% confidence. Conversion of effect estimates will be applied where necessary.

If the studies included in this systematic review are not sufficiently similar, non-statistical synthesis will be undertaken. This will be done via structured tabulation of results across studies. The results of the systematic review will be reported in a summary table, outlining the intervention methods used and the effects on the outcomes reported. There will also be an ordering of the studies within this table, depending on the certainty of the evidence presented in the study, the risk of bias via ROBINS-I assessment and the overall relevance and validity of outcome measures.

Exploration of heterogeneity among studies will be completed by using a forest plot. This is expected to be higher than normal due to the relative diversity associated with the types of studies involved in this review. Statistical heterogeneity will be analysed using the I^2 statistic. This is defined as the proportion of variation in effect estimates that is due to genuine variation between investigations rather than random sampling error. If meta-analysis is unsuitable, a forest plot will still be completed, however, with summary estimates suppressed.

Meta-biases

If more than 10 studies are included in this systematic review, asymmetry in a funnel plot testing treatment effect against study size will be used to explore possible publication bias. A subgroup analysis is not planned for this systematic review as it is anticipated that results for demographic subgroups will not be available as potential outcomes in this research area.

Confidence in cumulative evidence

Our level of confidence in the cumulative evidence produced by this systematic review will be assessed using the 'Grading of Recommendations, Assessment, Development and Evaluation' approach.[26] Two independent reviewers will classify the quality of evidence as very low, low, moderate or high by assessing study limitations, inconsistency of results, imprecision, reporting bias and indirectness of evidence.

Patient and public involvement

There was no specific patient or public involvement in the development of this protocol.

DISCUSSION

Interpretations of the outcomes of the interventions that will be assessed will carefully consider any risk of bias in individual studies, publication bias in meta-analysis and confidence in cumulative evidence. Interpretations of results will also consider the public healthcare context of the country in which the study took place, as this review is not restricted to a specific healthcare system.

Potential limitations of this review include language bias[27] due to only including English language publications and the potential low confidence in cumulative evidence due to the high heterogeneity expected with NRSIs and feasibility studies, possibly leading to the inability to engage in quantitative metasynthesis.

This review is timely as a recent systematic review[1] assessing the factors influencing DKA admissions identifies diagnostic delay as an issue which increases the risk of DKA admission. This review will assist in deciding which interventions generate meaningful impacts on reduction of the diagnostic delay interval, reducing the number of DKA admissions. Understanding the strengths and limitations of trialled interventions will also allow for optimisation of planned interventions to assist clinicians with making timely diagnoses as much as possible.

ETHICS AND DISSEMINATION

Ethics approval is not required for a systematic review. The information and data emerging from the systematic review will be disseminated via publication and conference presentation.

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Contributors CB wrote the protocol and is the guarantor of the review. CB and VB developed the search strategy. BH, MW and J-AM-N provided input to the research question and protocol development and provided feedback on the protocol.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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