PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Have interventions aimed at assisting general practitioners in facilitating earlier diagnosis of type 1 diabetes in children been successful in preventing acute complications ? A systematic review.
AUTHORS	Beccia, Chiara; McMorrow, Rita; Donald, Andrew; de Mendonça, Lucas; White, Mary; Hunter, Barbara; Manski-Nankervis, Jo-Anne

VERSION 1 - REVIEW

REVIEWER NAME	Majaliwa, Edna
REVIEWER AFFILIATION	Kilimanjaro Christian Medical University College
REVIEWER CONFLICT OF INTEREST	No competing interest
DATE REVIEW RETURNED	11-Mar-2024

GENERAL COMMENTS	Congratulation for the work done 1. Title: TITLE IS DIAGNOSIS OF T1DM but introduction is DKA which happens a week after diagnosis is this early? We may need to change the title. I will make an addition .....successful in preventing acute complications: a systematic review or any other way to reflect DKA 2. Abstract: Well written except: in results section were these communications from the GP TO SPECIALIST? or someone else like a nurse to specialist skipping the GP? Discussion part: the conclusion was titled discussion -as a result no conclusion appears but whatever is written, points to conlusion 3, Discussion: just a point of clarification? What was the indirect communication with the GPs?

REVIEWER NAME	Alassaf, A
REVIEWER AFFILIATION	The University of Jordan
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	18-Mar-2024

GENERAL COMMENTS	This systemic review for effect of interventions in general practice to reduce diagnostic delay of T1DM in children, was well-conducted and written, but in my opinion, in addition to the small number of publications (5), it included abstracts lacking clear methodologies. In addition, the main purpose of the review to see effect of interventions on number of patients with delayed diagnosis was not mentioned except foe 2 publications reviewed.

REVIEWER NAME	Townson, Julia
REVIEWER AFFILIATION	Cardiff University, Centre for Trials Research
REVIEWER CONFLICT OF INTEREST	N/A
DATE REVIEW RETURNED	22-Mar-2024

GENERAL COMMENTS	The manuscript is well written and the topic is an important one. I have listed my comments below:- 1) Abstract, Results states nine studies were included. This is not consistent with the main text/prisma flow diagram which states 8 studies were included in the review. 2) Discussion of abstract states 'Implementation of quality improvement interventions in GP settings for DKA prevention purposes is feasible.' I think this sentence should be removed or amended as the aim of the systematic review did not include an assessment of feasibility. 3) The outcomes described in the abstract are not consistent with the protocol paper e.g DKA rate. If the outcomes were amended following publication of the protocol paper I think this should be noted in the manuscript. 4) In the strengths and limitations of the study statement, it states 'This review assessed interventions to reduce diagnostic delay interval for paediatric type 1 diabetes in general practice.' I am not sure that this should be in the strength and limitations section as I think this is the aim of the systematic review. 5) I was surprised that some papers did not come up in your literature search, for example Lansdown (2012) Prevalence of ketoacidosis at diagnosis of childhood onset Type 1 diabetes in Wales from 1991 to 2009 and effect of a publicity campaign and Fritsch (2013) Diabetic ketoacidosis at diagnosis in Austrian children: a population-based analysis, 1989-2011 6) Please check the Darmonkow 2021 paper, I thought this included participants up to age 25 years, and those already diagnosed with type 1 diabetes? 7) It was not clear what was meant by direct and indirect communication? As in the Townson (2016) paper there was direct communication in the form of dedicated community liaison nurses who visited GP practices. 8) Under the sub heading Intervention types, page 9, line 37 - It is stated that 3 studies paired the GP intervention with a publicity campaign. I think Townson 2016 should also be included in this category. 9) It would be useful to include the raw numbers in Table 3 as large changes in DKA rate can be as a result of small numbers. 10) I think the conclusion should be revised. From the systematic review results I do not think that you can conclude that the interventions could positively change GP behaviour. This is reflected in the consistent rate of DKA reported in Cherubini's 2020 paper Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents. 11) In the Townson 2016 paper, it describes a GP advisory group who designed and determined the intervention. It would be good to note this, as you specifically mention this as a knowledge gap that has been identified.

	12) In the Prisma checklists please provide the page numbers where each item is reported. Minor typo 13) Page 17, line 43 'important' should be 'importance'

REVIEWER NAME	Levitsky, Lynne
REVIEWER AFFILIATION	Harvard Medical School
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	28-Mar-2024

GENERAL COMMENTS	The authors have previously published their intended methodology for this study. Unfortunately after carefully searching the literature they are able to identify only 5 full publications which in some ways address the question. One of them Darmonkow (ref 30) seems to address reduction in total DKA in a population of young people who may be new diagnoses or may be known individuals with DKA. Therefore it does not meet the primary objective of facilitating earlier diagnosis of T1D and preventing or ameliorating DKA. In addition Ahmed (27) demonstrated significant decreased severity of DKS with education but the decrease in DKA rate does not seem to be significant on my review of the paper. Towson (ref 31) describes the plans for such a study but does not seem to provide data. King ref 28) describes a multifaceted campaign which included but was not fully targeted to practitioner's offices. Three other reports are abstracts along and have not been subjected to full peer review. It does not seem they should be included in a review like this. The statistics and significance of findings in the papers included in this review need to be discussed-they are not- but there is a fair amount of redundancy. The authors rightfully point out that more targeted larger studies should be carried out to assess the efficacy of interventions which seem with limited data to be best when personalized. An enormous amount of time and space is devoted to describing the weeding out process of papers to be reviewed for this manuscript--this could be greatly reduced. Perhaps, since one of the best papers looked at reduction in DKA in all comers, it might be good to refocus not on new diagnosis, but on reduction in DKA in general.

REVIEWER NAME	Helmer, Stefanie Maria
REVIEWER AFFILIATION	University of Bremen
REVIEWER CONFLICT OF INTEREST	I have no competing interests to declare.
DATE REVIEW RETURNED	30-Apr-2024

GENERAL COMMENTS	The manuscript “Have interventions aimed at assisting general practitioners in facilitating earlier diagnosis of type 1 diabetes in children been successful? A systematic review. is of overall good methodological quality. The literature review follows PRISMA guidelines and study was previously registered and a study protocol was published.

	However, a few remarks could be made that should be noted for revision. Methods: The authors should mention in the appendix 1 how the search terms were connected within the search (as already shown in the study protocol). According to PRISMA, the search strategy for each database should be described, especially if there are substantial adaptations. Furthermore, it should be specified how grey literature were searched (information sources). It becomes not clear when conference abstracts were included and which information was assessed via email and how the information was included in the review. The data extraction is not explained and the data items are not displayed which is required according to PRISMA. Results: PRISMA diagram: The authors should specify why 2 studies were not retrieved. Tables: Did the authors order the studies 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 as indicated in their study protocol? If not please explain. The authors should explain the certainty of evidence or should explain why they did not report this information. Appendix: The PRISMA checklist should indicate where the reader can find the relevant information (page).

VERSION 1 – AUTHOR RESPONSE

#	**Reviewer 1**	Response from authors
1	Title: TITLE IS DIAGNOSIS OF T1DM but introduction is DKA which happens a week after diagnosis is this early? We may need to change the title. I will make an addition .....successful in preventing acute complications: a systematic review or any other way to reflect DKA	Thank you very much for your suggestion regarding our title. We agree that it would be clearer for the audience to amend our title, to reflect more adequately what we have written in the background section. We have amended our title to say: "Have interventions aimed at assisting general practitioners in facilitating earlier diagnosis of type 1 diabetes in children been successful in preventing acute complications? A systematic review"
2	Abstract: Well written except: in results section were these communications from the GP TO SPECIALIST? or someone else like a nurse to specialist skipping the GP? Discussion part: the	Thank you for your feedback, this will make our abstract clearer. Regarding the communicates from the GP, these were from the researchers to the GP, we have modified our abstract to include this. Regarding the discussion part reading like a

	conclusion was titled discussion -as a result no conclusion appears but whatever is written, points to conclusion	conclusion, we have changed the title of that section from discussion to conclusion to fix this.
3	Discussion: just a point of clarification? What was the indirect communication with the GPs?	Thank you for your feedback about this. We have updated our discussion section to specify what indirect communication with GPs involved (newsletters to practices, posters, etc).

#	**Reviewer 2**	Response from authors
1	This systemic review for effect of interventions in general practice to reduce diagnostic delay of T1DM in children, was well-conducted and written, but in my opinion, in addition to the small number of publications (5), it included abstracts lacking clear methodologies. In addition, the main purpose of the review to see effect of interventions on number of patients with delayed diagnosis was not mentioned except foe 2 publications reviewed.	Thank you for your feedback on our manuscript, we believe that it has given us a great opportunity to improve our work. The points regarding the limitations of our study are well taken, we agree with your assessment. First, you state that the small number of publications and inclusion of abstracts with lacking methodologies is a limitation. We agree that this limitation is significant and have amended our discussion to make this clearer. We have also made changes to our conclusion section where we are careful not to draw overstated conclusions that are not sufficiently supported by the evidence. You also state that the main purpose of the review was to assess the effect of interventions on the number of patients with delayed diagnosis, and you are correct in stating that this was not mentioned except for two publications that were included in the review. We also agree that this significantly limits the conclusions that we can make about a reduction in diagnostic delay following such interventions. In light of these comments, we have proposed that we amend our manuscript to emphasise a summary of interventions applied in general practice, rather than as an evaluation of the effectiveness of the interventions themselves. It seems that your comments, in combination with other reviewer comments, has allowed us to reconsider the limitations surrounding our

		findings. We will amend the relevant introduction, methodology, and discussion sections to emphasise that our results are a narrative summary and limit our conclusions regarding the effectiveness of the interventions. We do believe that, while including publications and abstracts with insufficient methodology, that our systematic review still holds immense value in the research field. This is because it is important to highlight the lack of interventions that specifically address diagnostic delay in this area, rather than solely DKA admissions. We also highlight important questions surrounding longevity and the importance of codesign with general practitioners, which is crucial to the success of future interventions in this field. As a result, we would like to compromise, and reframe our study as more of a summative review rather than an evaluative review. General practitioners are the first point of call for many patients at first diagnosis of diabetes, and our paper is crucially important in underlining the clear gaps in the literature with respect to co-designed, sustainable interventions that are targeted toward them. Overall, we agree with your advice, however, feel that our manuscript provides a significant contribution to the research field, despite a lack of sufficiency in results. We acknowledge that the limitations of the methodology significantly limit the applicability and validity of our conclusions, and have taken significant steps to acknowledge these limitations, decrease the extent to which our conclusions have been drawn, as well as to reframe our study as primarily summative of existing interventions and secondarily evaluative.

#	**Reviewer 3**	**Response from authors**
1	Abstract, Results states nine studies were included. This is not consistent with the main text/prisma flow diagram which states 8 studies were included in the review.	We have amended this error. Thank you.

2	Discussion of abstract states 'Implementation of quality improvement interventions in GP settings for DKA prevention purposes is feasible.' I think this sentence should be removed or amended as the aim of the systematic review did not include an assessment of feasibility.	This is a good point; we have removed this sentence.
3	The outcomes described in the abstract are not consistent with the protocol paper e.g DKA rate. If the outcomes were amended following publication of the protocol paper I think this should be noted in the manuscript.	Thank you for pointing this out. We have noted this change in the manuscript.
4	In the strengths and limitations of the study statement, it states 'This review assessed interventions to reduce diagnostic delay interval for paediatric type 1 diabetes in general practice.' I am not sure that this should be in the strength and limitations section as I think this is the aim of the systematic review.	Thank you for pointing this out, we have removed this statement from the strengths and limitations section of the manuscript.
5	I was surprised that some papers did not come up in your literature search, for example Lansdown (2012) Prevalence of ketoacidosis at diagnosis of childhood onset Type 1 diabetes in Wales from 1991 to 2009 and effect of a publicity campaign and Fritsch (2013) Diabetic ketoacidosis at diagnosis in Austrian children: a population-based analysis, 1989-2011	Thank you for identifying these papers. We have checked Covidence to ascertain whether they were identified in the search. The first one, Lansdown (2012) was identified within our search, but following a title and abstract review, we decided that it met our exclusion criteria. This is because we deemed posters in waiting rooms of general practices as insufficient to be deemed as targeting general practitioners specifically. The Fritsch (2013) study was not identified in our search, we thank you again for pointing out this paper. After having reviewed it, we also believe that it meets our exclusion criteria, as it describes 'broadly dispensing posters' as its main intervention method, which is not discussing an active consideration of general practitioners. We thank you for pointing these papers out, as we have had a second read of our methods section and it is unclear that this was part of our exclusion criteria. We have amended our methodology section so that this is clearer for the reader.
6	Please check the Darmonkow 2021 paper, I thought this included participants up to age 25 years, and	Thank you for identifying this. The authors had originally included the Darmonkow 2021 paper as it separately analysed DKA rate for patients in the 18-25 range, and included new onset type

	those already diagnosed with type 1 diabetes?	1 diabetes as a potential target for DKA reduction, as well as those with established diabetes. On a second review, we believe inclusion of this investigation is still required, as it does focus part of its interventions on promoting earlier diagnosis of type 1 diabetes. While it separates its analyses into paediatric and adult age groups, we do recognise that it does not separate the data into DKA admissions that were as a result of first diagnosis or repeat presentation with DKA following diagnosis. We believe that the limited number of studies included in this manuscript justify its inclusion. We will note that it does not separate repeat DKA hospitalisations from DKA hospitalisations at first diagnosis as an individual limitation in Table 4.
7	It was not clear what was meant by direct and indirect communication? As in the Townson (2016) paper there was direct communication in the form of dedicated community liaison nurses who visited GP practices.	Thank you for bringing this point of clarification to our attention. We have amended our definitions of indirect and direct communication with general practitioners to be clearer for the reader.
8	Under the sub heading Intervention types, page 9, line 37 - It is stated that 3 studies paired the GP intervention with a publicity campaign. I think Townson 2016 should also be included in this category.	Thank you for identifying this, we have amended the intervention types section to include the Townson 2016 study.
9	It would be useful to include the raw numbers in Table 3 as large changes in DKA rate can be as a result of small numbers.	Thank you for pointing this out, it will certainly enhance clarity for the reader. We have amended Table 3 to include raw numbers to ensure that the change in DKA rate is not artificially inflated by the usage of percentages.
10	I think the conclusion should be revised. From the systematic review results I do not think that you can conclude that the interventions could positively change GP behaviour. This is reflected in the consistent rate of DKA reported in Cherubini's 2020 paper Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents.	Thank you for this feedback. We agree that our conclusions are overstated given not only the limited information that we derived in our review, but also the consistent rate of DKA reported in Cherubini’s 2020 paper. Thank you for bringing this paper to our attention, as we are able to include some discussion regarding the longevity and sustainability of these interventions in different healthcare contexts.

11	In the Townson 2016 paper, it describes a GP advisory group who designed and determined the intervention. It would be good to note this, as you specifically mention this as a knowledge gap that has been identified.	Thank you for this feedback. This is a good point. We have revised part of our discussion section to discuss whether included studies consulted with general practitioners prior to implementation of the intervention. We believe that this will greatly enhance the quality of our discussion.
12	In the Prisma checklists please provide the page numbers where each item is reported.	Thank you, we have provided an updated Prisma checklist with the page numbers where each item is reported.
13	Page 17, line 43 'important' should be 'importance'	Thank you, we have amended this error.

#	**Reviewer 4**	**Response from authors**
1	The authors have previously published their intended methodology for this study.	Thank you very much for your feedback, we believe that it greatly enhances our paper. We have considered your feedback deeply and have greatly amended our conclusions to refocus the goal of our study to be summative rather than evaluative. We have also refocused our discussion section to discuss the results as a demonstration of the clear gap in literature rather than evaluating intervention types themselves, as there is a great paucity of information in the studies included in this review. Further responses to your comments are below.
2	Unfortunately after carefully searching the literature they are able to identify only 5 full publications which in some ways address the question. One of them Darmonkow (ref 30) seems to address reduction in total DKA in a population of young people who may be new diagnoses or may be known individuals with DKA. Therefore it does not meet the primary objective of facilitating earlier diagnosis of T1D and preventing or ameliorating DKA. In addition Ahmed (27) demonstrated significant decreased severity of DKS with education but the decrease in DKA rate does not seem to be significant on my review of the paper. Towson (ref 31) describes the plans for such a study but does not seem to provide data. King ref 28)	Thank you very much for your feedback and for evaluating each of the included publications one by one. We agree that each publication has its limitations and do not fully address our question in cases and agree that this significantly limits the conclusions that we can draw as a result. We believe that this research is still significant despite its clear limitations, as it highlights a clear research gap and areas for future direction which are significant. However, we do want to address your concerns about each of the publications to ensure that these are adequately communicated in the manuscript, as we agree that our communication of this has not been adequate so far from the reader’s perspective.

	describes a multifaceted campaign which included but was not fully targeted to practitioner's offices. Three other reports are abstracts along and have not been subjected to full peer review. It does not seem they should be included in a review like this.	Regarding the Darmonkow paper, thank you for identifying this. The authors had originally included the Darmonkow 2021 paper as it separately analysed DKA rate for patients in the 18-25 range, and included new onset type 1 diabetes as a potential target for DKA reduction, as well as those with established diabetes. On a second review, we believe inclusion of this investigation is still required, as it does focus part of its interventions on promoting earlier diagnosis of type 1 diabetes. While it separates its analyses into paediatric and adult age groups, we do recognise that it does not separate the data into DKA admissions that were as a result of first diagnosis or repeat presentation with DKA following diagnosis. We believe that the limited number of studies included in this manuscript justify its inclusion. We will note that it does not separate repeat DKA hospitalisations from DKA hospitalisations at first diagnosis as an individual limitation in Table 4. You are correct in identifying that the Ahmed (27) paper did not significantly reduce DKA presentations following the intervention. We recognise that we haven't listed this as a specific limitation of the publication and may have overstated the conclusions drawn because of the slight reduction reported in the Ahmed study. As a result, in the revised paper we have included a table outlining the limitations of each individual study and have removed conclusions regarding the effectiveness of these interventions. This is because, as you have accurately identified, we (1) have highly limited data to draw from, and (2) the reduction in DKA rate is not significant in this publication. You are correct that the Townson study (31) does not provide quantitative data that pertains to a change in rate of DKA following the intervention. However, it does include qualitative data from general practitioners that evaluates the success of the prevention interventions and educational interventions. We believe the results generated from this study are important to inform the design of interventions in the future, as this study includes the voice of the general

		practitioner, which is critically underrepresented in the literature. Despite this, we do agree that we cannot draw conclusions about the performance of this study on the reduction of the rate of DKA or diagnostic delay, and therefore have reduced any conclusions we have made about the interventions in this study. We have also included this as a limitation in the new limitations table that we have included in the paper to clarify this for the reader. The King study is multifaceted, as it targets schools, communities and general practitioners. We decided that it is eligible for inclusion, as there is active involvement of the general practitioner in the intervention. For example, the provision of blood glucose and ketone monitors, as well as letters to each general practitioner explaining the intervention. Finally, the three abstracts are limited in their methodologies and have not been peer reviewed. We agree that this limitation is significant, and understand that this draws a line of questioning into the validity of their inclusion in the manuscript. We agree that due to the highly limited information provided, that we can only provide summative information here regarding the interventions that were attempted in the community, and should not draw any conclusions regarding the studies that were included as abstracts. We have amended our results and discussions section to reflect this, and refocused our study to be a summative review of interventions applied in general practice, highlighting the significant gaps in literature in this field, as well as key future directions. We believe that your feedback has greatly improved our manuscript, particularly as it pertains to the discussion and conclusion sections. We believe that we have enhanced the integrity and the findings of our investigation because of the changes made to our manuscript.
3	The statistics and significance of findings in the papers included in this review need to be discussed-they are	Thank you for indicating this. We have amended the results section of our manuscript to evaluate the significance of findings from the individual papers. We have also reviewed the manuscript

	not- but there is a fair amount of redundancy.	to identify and eliminate redundant information, to ensure that it is concise and coherent for the reader.
4	The authors rightfully point out that more targeted larger studies should be carried out to assess the efficacy of interventions which seem with limited data to be best when personalized. An enormous amount of time and space is devoted to describing the weeding out process of papers to be reviewed for this manuscript-- this could be greatly reduced.	Thank you for identifying this, we have reduced this section to ensure it is succinct for the reader.
5	Perhaps, since one of the best papers looked at reduction in DKA in all comers, it might be good to refocus not on new diagnosis, but on reduction in DKA in general.	We agree that interventions to reduce DKA in all comers would make for an interesting paper and would be significant. However, our focus for this manuscript is specifically to address the challenge of DKA at first presentation.

#	**Reviewer 5**	Response from authors
1	The authors should mention in the appendix 1 how the search terms were connected within the search (as already shown in the study protocol). According to PRISMA, the search strategy for each database should be described, especially if there are substantial adaptations. Furthermore, it should be specified how grey literature were searched (information sources). It becomes not clear when conference abstracts were included and which information was assessed via email and how the information was included in the review. The data extraction is not explained and the data items are not displayed which is required according to PRISMA.	Thank you very much for your feedback, we believe it has greatly enhanced our manuscript. We have included a detailed search strategy in our Supplementary File to outline how search terms have been connected as well as what was used for all other databases. We also have updated our methodology section to describe more specifically how grey literature were searched. We have updated our methodology section to also include which information was assessed via email and how we included this information in the review. We have also amended our methodology section to explain the data extraction process more clearly and have included a template for data extraction in a new supplementary file.

2	PRISMA diagram: The authors should specify why 2 studies were not retrieved.	Thank you, we have updated the diagram to specify why two studies were not retrieved.
3	Results: Tables: Did the authors order the studies 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 as indicated in their study protocol? If not please explain. The authors should explain the certainty of evidence or should explain why they did not report this information.	Thank you for your question regarding the results table. We did indeed reorder the studies in the table according to the certainty of evidence, but as you rightly picked up, we did not make this clear to the reader. We have amended the results table to make this clear to the reader. We have also amended our results section to explain why we did not evaluate the certainty of cumulative evidence in this review.
4	Appendix: The PRISMA checklist should indicate where the reader can find the relevant information (page).	Thank you, we have updated the PRISMA checklist to indicate where the reader can find the relevant information.

VERSION 2 - REVIEW

REVIEWER NAME	Townson, Julia
REVIEWER AFFILIATION	Cardiff University, Centre for Trials Research
REVIEWER CONFLICT OF INTEREST	N/A
DATE REVIEW RETURNED	25-Jul-2024

GENERAL COMMENTS	I am happy with all the corrections and responses of the authors to my comments