PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.
AUTHORS	Shields, Beverley; Peters, Jaime; Cooper, Chris; Lowe, Jenny; Knight, Bridget; Powell, Roy; Jones, Angus; Hyde, Chris; Hattersley, Andrew

VERSION 1 - REVIEW

REVIEWER	Zhiguang Zhou The Second Xiangya Hospital
REVIEW RETURNED	13-Jul-2015

GENERAL COMMENTS	Misclassification of diabetes is widespread (7-15% of cases), resulting in patients receiving inappropriate treatment. This systemic review collected diagnostic papers from 1979. The key differentiation criteria used in this review is insulin insufficiency (C-peptide). It was the first time to use the evidence based method to explore the possible clinical features, which could be used to differentiate type 1 and type 2 diabetes. The final finding is that age at diagnosis and time to insulin were consistently the most discriminatory criteria. BMI, despite being widely used in clinical practice, adds little to these 2 criteria. Overall, the manuscript is good written and the systemic review is strictly carried out by its rule. However, there are still some questions for the authors: 1. Whether it is realistic to diagnose type 1 and type 2 diabetes only with clinical features? The fundamental of the manuscript is that type 1 and type 2 diabetes should be differentiated in practice. However, in real world, the situation is that the grey area between type 1 and type 2 increased a lot. Some of the diabetes patients has the clinical feature similar to type 2 diabetes but with the etiology similar to type 1 diabetes. Approximately, there are about 10% newly diagnosed type 2 diabetes patients with positive islet autoantibodies, which is the crucial lab marker for type 1 diabetes. It is now hard to use only the clinical feature and also it is also not accurate to use only the clinical feature to diagnosis type 1 and type 2 diabetes. Assaying C-peptide, islet autoantibodies and together with the clinical features and follow up interviews may be more realistic to make a correct diagnosis of diabetes. 2. Author only use insulin deficiency (C-peptide) as the criteria to differentiate type 1 and type 2 diabetes. How about the islet autoantibodies? Some of the slowly developed type 1 diabetes (or called latent autoimmune diabetes in adults, LADA), won't show insulin deficiency at the diagnosis, but with only positive islet autoantibodies. Obviously, insulin deficiency is not the only differentiate criteria for type 1 and type 2 diabetes.

	3. Limitation as the author mentioned by themselves. Small paper numbers and the heterogeneity of the 11 studies make the evidences is not as strong as we thought. The portion of insulin insufficiency is from 7%-69%. Therefore, although the manuscript is well designed and written, without new findings for this systemic review, I don't agree it could be published in BMJ.

REVIEWER	Craig Jefferies Starship Children's Health Auckland New Zealand
REVIEW RETURNED	30-Jul-2015

GENERAL COMMENTS	this article entitle "Can clinical features be used to differentiate Type 1 from Type 2 diabetes?" is an extremely well written, structured and grammatically correct work. My major concern as they alude to in the paper is that the systematic review of this topic is hampered by the large date range, the overall paucity of studies. The key driver for this study was the use of C peptide as the main outcome measure, and few studies had this. The take home message is that less and 30-40 years and time to insulin should strongly indicate that this is T1DM not T2DM. Irrespective of BMI and that as they state in p15 the other need is better critical inclusion criteria for such studies in the future.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Whether it is realistic to diagnose type 1 and type 2 diabetes only with clinical features?
The fundamental of the manuscript is that type 1 and type 2 diabetes should be differentiated in practice. However, in real world, the situation is that the grey area between type 1 and type 2 increased a lot. Some of the diabetes patients has the clinical feature similar to type 2 diabetes but with the etiology similar to type 1 diabetes. Approximately, there are about 10% newly diagnosed type 2 diabetes patients with positive islet autoantibodies, which is the crucial lab marker for type 1 diabetes. It is now hard to use only the clinical feature and also it is also not accurate to use only the clinical feature to diagnosis type 1 and type 2 diabetes. Assaying C-peptide, islet autoantibodies and together with the clinical features and follow up interviews may be more realistic to make a correct diagnosis of diabetes.

We agree with the reviewer that there is a grey area between Type 1 and Type 2 diabetes and we acknowledge that islet autoantibodies are a biomarker that may aid differential diagnosis of Type 1 and Type 2 diabetes. Islet autoantibodies, however, are not commonly measured in clinical practice and their routine use is not advocated in guidelines. Therefore, we aimed to concentrate on clinical features alone in this paper. However, we do recognise that there may be a role for islet autoantibodies in the classification of diabetes subtypes, and so this is forming a second systematic review, which is now underway and we have registered the protocol on Prospero. We have now added this to page 7, para 1.

2. Author only use insulin deficiency (C-peptide) as the criteria to differentiate type 1 and type 2 diabetes. How about the islet autoantibodies? Some of the slowly developed type 1 diabetes (or

called latent autoimmune diabetes in adults, LADA), won't show insulin deficiency at the diagnosis, but with only positive islet autoantibodies. Obviously, insulin deficiency is not the only differentiate criteria for type 1 and type 2 diabetes.

We agree with the reviewer that insulin deficiency is not the only differential criteria for Type 1 and Type 2 diabetes from a purely aetiological point of view. However, we need a gold standard which is most relevant to clinical practice and it is insulin deficiency, rather than islet autoimmunity itself, that determines differences in treatment requirement between type 1 and 2 diabetes. Furthermore islet autoantibodies are a very imperfect marker for classification of diabetes given high false negative rates and moderately high reported prevalence (for GAD) in non insulin requiring patients. We have tried to emphasise this further in the introduction (page 5, para 2). We do acknowledge the limitations of C-peptide at diagnosis, however, and have added this to the discussion (page 16, paras 2 and 3).

3. Limitation as the author mentioned by themselves. Small paper numbers and the heterogeneity of the 11 studies make the evidences is not as strong as we thought. The portion of insulin insufficiency is from 7%-69%.
Therefore, although the manuscript is well designed and written, without new findings for this systemic review, I don't agree it could be published in BMJ.

We agree that this review is largely limited by the heterogeneity of studies, as described in our discussion (page 14). Although we provide no definitive clinical criteria, we have performed the first systematic review of the current evidence base, which highlights the real need for further work in this area.

Reviewer: 2

Dear Editor this article entitle "Can clinical features be used to differentiate Type 1 from Type 2 diabetes?" is an extremely well written, structured and grammatically correct work.
My major concern as they alude to in the paper is that the systematic review of this topic is hampered by the large date range, the overall paucity of studies. The key driver for this study was the use of C peptide as the main outcome measure, and few studies had this.

Many thanks for these comments. We agree that the small number of studies and considerable heterogeneity between them is the major limitation of this review and have described these issues in the Discussion (page 14, paras 2 and 3). As the most important reason for classification is to ensure appropriate treatment, and insulin deficiency is the driver behind the difference in treatment decisions between Type 1 and Type 2 diabetes, insulin deficiency, as measured by C-peptide, was felt the most appropriate reference standard, even though relatively few studies reported this as their outcome.

The take home message is that less and 30-40 years and time to insulin should strongly indicate that this is T1DM not T2DM. Irrespective of BMI and that as they state in p15 the other need is better critical inclusion criteria for such studies in the future.

This is an excellent summary of the take home message of our paper and we have tried to bring out these key points in the conclusion of our paper (page 17, para 1) and abstract (page 3)