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# Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.



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**Title: Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.**

**Short title:** Clinical criteria for Type 1 & Type 2 diabetes

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**Abstract: (297 words).**

Objective: Clinicians predominantly use clinical features to differentiate Type 1 from Type 2 diabetes yet there are no evidence-based clinical criteria to aid classification of patients. Misclassification of diabetes is widespread (7-15% of cases), resulting in patients receiving inappropriate treatment. We sought to identify which clinical criteria could be used to discriminate Type 1 and Type 2 diabetes.

Design: Systematic review of all diagnostic accuracy studies published since 1979 using clinical criteria to predict insulin deficiency (measured by C-peptide).

Data sources: 14 databases including: MEDLINE, MEDLINE in Process and EMBASE. The search strategy took the form of: (terms for diabetes) AND (terms for C-Peptide).

Eligibility criteria: Diagnostic accuracy studies of any routinely available clinical predictors against a reference standard of insulin deficiency defined by cutoffs of C-peptide concentrations. No restrictions on race, age, language, or country of origin.

Results: 10,917 abstracts were screened, and 231 full texts reviewed. 11 studies met inclusion criteria, but varied by age, race, year, and proportion of participants who were C-peptide negative. Age at diagnosis was the most discriminatory feature in 7/9 studies where it was assessed, with optimal cutoffs (>70% mean sensitivity and specificity) across studies being <30y or <40y. Use of/time to insulin treatment and BMI were also discriminatory. When combining features, BMI added little over age at diagnosis and/or time to insulin (<1% improvement in classification).

Conclusions: Despite finding only 11 studies, and considerable heterogeneity between studies, 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. The criteria identified are similar to the RCGP/NHS Diabetes classification guidelines, which use age at diagnosis <35y and time to insulin <6m. Until further studies are carried out, these guidelines represent a suitable classification scheme.

Systematic Review Registration: PROSPERO reference CRD42012001736

**Article summary**

**Strengths and limitations of this study:**

*Strengths:*

- We have carried out a comprehensive and robust systematic review in accordance with PRISMA guidelines and our initial published protocol.
- We screened a large number of literature sources, and all reviewing and data extraction was carried out in duplicate independently by two authors (BS and JP).

*Limitations:*

- Considerable heterogeneity across studies precluded a formal meta-analysis
- A limited number of studies were found meaning there is still considerable uncertainty around criteria for classification of Type 1 and Type 2 diabetes
- Variability in the reference standard of insulin deficiency across studies also led to further uncertainty around findings limiting direct usefulness of criteria

**Background:**

Correct classification of a patient's diabetes is crucial for ensuring they receive the most appropriate treatment and management. Current guidelines for the treatment of diabetes are specific to Type 1 and Type 2 diabetes and these show marked differences[1-4], reflecting the difference in endogenous insulin production between the two subtypes. Patients with Type 1 diabetes rapidly develop severe insulin deficiency, leading to high glycemic instability, and so require accurate insulin replacement (such as multiple injections and carbohydrate counting), and have poor response to non insulin therapies[3 5]. Patients with Type 2 diabetes still continue to produce substantial amounts of their own insulin, and, therefore, respond to non insulin therapy, have more stable glycemia and, if insulin treatment is needed, may achieve good control with non-physiological insulin regimes[6 7].

Currently, there are no published, evidence based, guidelines or criteria for diabetes classification, despite the importance for patient management. Guidance on the classification of the two types of diabetes from major health organisations is limited, and focuses on etiology[8 9], whereas it is insulin production that is the driver for informing treatment decisions. Insulin deficiency/production can be assessed by measurement of C-peptide in either blood or urine[10], but it is rarely measured in clinical practice and current guidelines for diabetes management do not recommend its routine use[1 3 11]. Classification is based primarily on clinical judgement, with younger slimmer patients tending to be classed as Type 1, and older, more obese patients diagnosed as Type 2[8]. However, with obesity increasing in the population and the resulting increase in Type 2 diabetes in the young, this traditional distinction has become less clear[12 13].

Misclassification of diabetes has been shown to occur in 7-15% of cases[13-15], and these studies are likely to underestimate the problem, as they only use clinical "clues" as their reference standard.

The current practice based on etiological guidelines and clinical opinion is clearly insufficient. Pragmatic guidelines on diabetes classification have been developed by NHS Diabetes and The Royal College of General Practitioners in the UK, but are taken from consensus expert clinical opinion rather than being evidence-based[13].

In order to determine evidence based criteria that could be used to classify the two main forms of diabetes, an appropriate gold standard is necessary. The most important reason for classifying patients is to ensure appropriate treatment and management, and the main factor determining this is the difference in endogenous insulin production between patients with Type 1 and Type 2 diabetes. Therefore, long term insulin deficiency represents an acceptable reference standard for Type 1 diabetes. This is likely to be preferable to using markers of the autoimmune process associated with Type 1 diabetes, as this can be measured by a number of different islet autoantibodies, none of which discriminate perfectly[16], and most importantly, treatment requirements are based on insulin deficiency rather than autoimmunity.

We aimed to systematically review the literature to identify clinical criteria, predictive of severe insulin deficiency, that could be used to discriminate Type 1 diabetes from Type 2 diabetes and inform evidence based guidelines for the classification of diabetes.

**Methods**

We followed the PRISMA guidelines for the reporting of systematic reviews. The original protocol has been published[17] and is registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/ reference CRD42012001736).

*Data sources and search strategy*

14 databases were searched systematically, including MEDLINE, MEDLINE in Process and EMBASE. The search strategy took the form of: (terms for diabetes) AND (terms for C-Peptide). Searches were limited to human only populations and from 1979 since that was when the original classification scheme was proposed by the National Diabetes Data Group[18]. Searches were not limited by language or study design.

Searches were also carried out on the Conference Proceedings Citation Index as well as the proceedings of the American Diabetes Association, the European Association for the Study of Diabetes, and Diabetes UK. BL Ethos was also searched for theses. Web-searching was conducted, including web-site specific searches of WHO and NICE. Forwards and backwards citation chasing was conducted on all studies included at full-text. The full search strategies are recorded in the online supplemental material (Supplemental Search Annex). Searches were initially performed in October 2012 and were updated on 03/04/14 to capture any additional studies that may have been carried out since the beginning of the review.

*Study selection:*

A two-stage screening process was undertaken. In Stage 1, after removing duplicates, two reviewers (BS and JP) independently screened the titles and abstracts of all references against the inclusion and exclusion criteria. In Stage 2, full texts were retrieved on all studies included at the first screening stage and were independently screened (by BS and JP). Authors of included conference abstracts were searched to determine whether a full article had subsequently been published. Any discrepancies between the two reviewers were discussed and resolved by consensus, or in discussion with a third reviewer (RP).

*Inclusion and exclusion criteria*

Included studies comprised diagnostic accuracy studies of clinical predictors of insulin deficiency, with the reference standard of insulin deficiency being defined by cutoffs of C-peptide results. All measurements of C-peptide and all cutoffs for insulin deficiency were included. Clinical predictors were defined as any routinely measured clinical feature and studies were eligible if there was a cutoff for that clinical predictor assessed against the measure of insulin deficiency. There were no restrictions on race, age, or country of origin. Studies examining islet autoantibodies only were excluded as they are not routinely measured. Studies where patients had known causes of diabetes, e.g. monogenic, secondary or syndromic diabetes, were excluded.

*Data extraction*

For all studies meeting the inclusion and exclusion criteria, data were extracted independently by both reviewers (BS and JP). Data extraction forms were developed and piloted prior to the review. Key details of population (age, sex, country, race, year), diabetes (definition of diabetes, treatment, subgroups), reference standard (type of sample, stimulation, assay, cutoff used), and clinical predictors (which predictors were included, how they were measured, the cutoffs used) were recorded. All C-peptide cutoffs were converted to the fasting serum equivalent to allow direct comparison[10]. Two-by-two tables were extracted where possible to determine the proportion of patients who were C-peptide negative/positive (i.e. below/above the cutoff) and the sensitivity, specificity, positive and negative predictive values of the clinical characteristics at reported cut-offs.

*Quality assessment*

Both reviewers (BS and JP) assessed quality independently and discrepancies were resolved by consensus. Quality assessment forms, based on the criteria set out in QUADAS-2[19], were developed and piloted prior to review. These criteria included assessment of internal and external validity of patient selection, the clinical predictors, and patient flow and timing. Variability in the

measurements for the reference standard was assessed separately. Further details are available in the online supplemental material.

*Data synthesis*

Due to the considerable heterogeneity between the studies identified, meta-analysis, as proposed in our original protocol, was not appropriate. Data synthesis is, therefore, largely descriptive with summary data presented. Criteria with a mean of sensitivity and specificity >70% (equivalent to an ROC AUC of 0.7) were considered clinically useful. Ranking of the discriminatory ability of criteria *within* studies was used to compare their relative performance.

*Reporting bias*

No formal assessment of publication bias was undertaken due to heterogeneity between studies and the small number of included studies. We did perform a comprehensive and exhaustive search including grey literature, however it cannot be ruled out that our systematic review is affected by reporting biases.

**Results:**

*Initial screening*

Figure 1 shows the flow diagram of citations found. 10,917 records were identified from database searches and a further 148 sources were identified from grey literature searches. After title and abstract screening, 194 articles were deemed potentially relevant. Following full-text screening, 9 studies were identified as eligible based on our inclusion criteria[20-28] (for further details see online supplemental material).

Backward and forward citation searching was carried out on the 9 included references, and conference abstracts were followed up, identifying a further 43 studies for full text review, one of which[29] met our inclusion criteria. In April 2014, an update search was performed yielding a further 2101 references for screening. 36 of these were identified by the 2 reviewers as requiring full text review, and 1 of these fitted inclusion criteria[30]. Thus, 11 articles contribute to this systematic review.

*Data Extraction and Quality Assessment*

There was considerable heterogeneity across the included studies (see Supplemental Table 1). The 11 included studies spanned a wide range of years (1981-2013). Studies varied in terms of race, age group, and subgroups of diabetes studied. One study included only patients with end stage renal disease[21], whereas it was a specific exclusion criterion for another study[27]. Three studies focused on insulin treated patients only[23 28 29], whereas the other studies either included all patients regardless of treatment or did not report on treatment. Sample size ranged from <100[21 28 30] to >3000[24]. The proportion of patients classified as insulin deficient (based on the reported C-peptide cutoff in each paper) also varied (median (range) 40% (7% to 69%)), reflecting differing inclusion criteria across studies altering the proportions with different forms of diabetes across the studies.

Quality assessment of the included studies is summarized in Supplemental Table 2. In general, there was a low risk of bias in terms of patient selection and patient flow/timing. Two studies were at high risk of bias[21 28] in terms of the clinical criteria used as these were internally derived, so diagnostic performance is likely overestimated in these cases[31]. In terms of external validity, studies were all applicable to our broad research question but most restricted inclusion criteria to a subset of the diabetic population.

The reference standards varied in terms of sample provided, timing of sample in relation to meal stimulation, and cutoffs for C-peptide (Supplemental Table 3). Five studies report deriving their cutoffs from previous papers[20 21 24 28 29]. Two studies derived the cutoff used from their own data[26 27], potentially introducing bias, although the cut-offs were comparable to those derived from the literature. Despite the variation in measurements, all were appropriate to classify insulin deficiency and cutoffs were largely comparable with most approximating 0.2nmol/l[20 21 23-25 27 29], and 4 studies using a slightly more conservative cutoff (0.03-0.08nmol/l) [22 26 28 30]. Only one study measured C-peptide and clinical features at diabetes diagnosis[30]. All other studies were cross-sectional with varying duration of diabetes.

*Data synthesis*

Due to the heterogeneity across studies, particularly in terms of inclusion criteria, formal quantitative meta-analysis was not appropriate. Therefore, data synthesis is largely descriptive and more qualitative summaries are presented.

*Age at diagnosis, BMI, insulin treatment/time to insulin are consistent predictors of insulin deficiency across studies.*

Age at diagnosis (9 studies), measures of obesity (including BMI, or percentage desirable weight in earlier studies) (8 studies) and either time to insulin treatment (5 studies) and/or use of insulin treatment (3 studies) were identified as consistent clinical criteria predictive of insulin deficiency (Table 1). In all studies reporting these criteria, younger age at diagnosis, slimmer BMI and shorter time to insulin was used to define insulin deficiency.

Absence of each of acanthosis nigricans and hypertension were predictive of insulin deficiency (overall correct classification rates of 61% and 72%, respectively), but these were only assessed in

one study[30]. Other measures were available in four studies[21 25 26 30] (including history of diabetic ketoacidosis[21 25] or ketonuria[21], history of hypoglycemia[26], speed of onset of diabetes[25], long term complications[21], polyuria[21], weight loss[21], post-Sustacal glucose[26], serum creatinine[26], diabetes in a first degree relative[30], and history of poor control[26]), but they were either not discriminatory, or they contributed very little individual discriminatory power to an overall algorithm.

*Age at diagnosis cutoffs better predicted insulin deficiency than cutoffs of BMI or time to insulin*

When comparing discriminative ability of the most commonly reported criteria *within* studies, age at diagnosis, at the cutoff described in the individual study, correctly classified more patients than the other clinical features (most discriminatory criteria in 7/9 studies). Time to insulin/insulin treatment was the next best predictor, and BMI (or equivalent) was the weakest of the significant predictors (Table 1).

*Cutoffs for age at diagnosis, BMI and time to insulin were fairly consistent across studies*

Cutoffs with the best combination of sensitivity and specificity (mean of sensitivity and specificity >70%) were similar across studies. For predicting insulin deficiency, the best cutoffs for age at diagnosis were <30 yrs (2 studies) or </<=40yrs (4 studies). For time to insulin, <1 year (1 study) or </<=2 years (2 studies) were the best cutoffs, although longer cutoffs were not assessed in any of the studies identified. For BMI, cutoffs <27kg/$m^2$ (1 study) and <28kg/$m^2$ (3 studies) were most useful (see Table 2). Extracted 2 x 2 tables are presented Supplemental Tables 4.

*BMI cutoffs provide little improvement in classification in addition to age at diagnosis and insulin use/time to insulin criteria*

Combinations of cutoffs did not consistently improve the overall rate of classification. The addition of BMI did not improve classification over age at diagnosis and/or use of/time to insulin treatment in

all 5 studies where these combinations were reported (<1% improvement in classification; see Table 3). The addition of insulin treatment or time to insulin criteria improved classification over using age at diagnosis alone in 3/5 studies where both were reported (see Table 3). Extracted 2 x 2 tables and summary statistics are presented in Supplemental Tables 4 and 5.

## Discussion

### Principal findings

*Few studies have robustly assessed utility of clinical features in diagnosing diabetes subtype*

There were only 11 appropriate studies that examined which clinical characteristics could discriminate between Type 1 and Type 2 diabetes, using the reference standard of insulin deficiency. This is a remarkably low number of studies considering the vast majority of the >200M patients with diabetes will be classified into Type 1 or Type 2 on the basis of clinical features alone and an incorrect classification will result in inappropriate treatment.

*Age at diagnosis was the most discriminatory clinical feature*

Age at diagnosis, time to insulin and BMI consistently emerged as the main discriminatory clinical criteria despite the considerable heterogeneity of the included studies. Age at diagnosis was the best discriminatory criteria with diagnosis either below 30 or below 40 years being predictive of T1D. In terms of providing useful criteria for clinical practice, based on the current available evidence, this would suggest clinicians should place more emphasis on age than obesity when diagnosing diabetes subtype, but exercise caution when classifying patients diagnosed between the ages of 30 and 40 where further investigation is likely to be necessary.

*Time to insulin treatment is a useful discriminator, but biased by physician opinion*

Commencing insulin treatment before 2 years did slightly improve discrimination over age of diagnosis (Table 3). However, treatment assignment can clearly not be used to define initial treatment, which is one of the major reasons for determining diabetes subtype. Treatment decisions are physician-dependent, as well as disease-dependent, so will vary between clinicians.

*BMI discriminatory but adds little over age at diagnosis*

BMI provided <1% improvement in classification over age at diagnosis or age at diagnosis and time to insulin. Clinicians often use obesity as a marker to indicate Type 2 diabetes, but our findings suggest using this is unlikely to be helpful over and above using age at diagnosis.

*Other may not be sufficiently discriminatory*

Other measures were less often studied. Acanthosis nigricans and hypertension did discriminate C-peptide positive from C-peptide negative patients, but these were only assessed in one study. Other features were either not discriminatory or only contributed weakly to an algorithm, and therefore unlikely to be useful in practice. These measures included features of diagnosis such as diabetic ketoacidosis, ketonuria, and rapid onset of symptoms including weight loss. In fact, in the two studies examining only patients presenting with DKA, 40% and 46% were C-peptide positive[20 30], suggesting DKA is not useful in its own right for classifying a patient as having Type 1 diabetes.

**Strengths and weaknesses**

*Strengths:*

We have carried out a comprehensive and robust systematic review in accordance with PRISMA guidelines and our initial published protocol[17]. We screened a large number of literature sources,

and all reviewing and data extraction was carried out in duplicate independently by two authors (BS and JP).

*Limitations:*

Heterogeneity across studies could have influenced the diagnostic performance of cutoffs identified and so precluded formal meta-analysis. There were 4 key areas in particular, where heterogeneity was apparent: 1) The proportion of insulin deficient patients varied considerably across the studies (range 7-69%), reflecting major differences in inclusion criteria for each study, and varying proportions of Type 1 and Type 2 diabetes in the study populations. 2) Studies spanned over 30 years (1981-2013) and there have been considerable changes in the phenotype of Type 1 and Type 2 diabetes in this time. With the rising prevalence of obesity in the population, Type 1 patients are now more likely to be obese than in the past, and Type 2 diabetes has become more common in young adults. 3) Renal disease is known to impact on C-peptide clearance, so differences were likely in the studies excluding patients with renal disease[24 27], compared with those exclusively examining those with ESRD[21]. 4) Ethnicity differed across studies, from populations that were predominantly Caucasian[22 26], to those predominantly Hispanic and/or Black African[30]/African American patients[20 24]. Despite the considerable differences in studies, however, there were consistencies in both the criteria identified and the most discriminatory cutoffs across the different populations.

The small number of studies and the heterogeneity between them means there is still uncertainty around the usefulness of the criteria and cutoffs proposed, and highlights a clear need for further work in this area. This review provides a strong starting point from which to develop future prediction criteria.

Differences in the reference standards (e.g. in the samples, stimuli, assay used, and cutoffs used) highlighted problems with our reference standard for Type 1 diabetes. However, although cutoffs were derived in a variety of ways, they were largely comparable and appropriate for detecting insulin deficiency in the populations of interest. Where more than one cutoff was used[23 25 26 29], this made little difference (<12%) to the proportion of patients classified and the cutoffs identified. These differences represent potential issues with using our "gold standard" for insulin deficiency when aiming to classify Type 1 diabetes. We would therefore suggest caution in future studies when classifying patients close to the proposed C-peptide cutoff.

*Other forms of diabetes*

We have only considered the two main forms of diabetes for which there are clear national and international treatment guidelines. Rarer subtypes are not considered here. Other forms of diabetes, such as LADA, are not included in international guidelines, and appropriate treatment would be guided by insulin deficiency, our gold standard. Further work would be needed to derive criteria for a "grey area" where diagnosis of subtype is less certain and further investigations would be required to aid classification.

**Implications and Future work:**

Evidence-based guidelines on the classification of T1D and T2D need to include clinical criteria on how the diagnosis should be made. This is a major omission in current national and international guidelines for diabetes. The evidence as identified in this review suggests age at diagnosis and time to insulin (when available) are essential components as they contribute most to the predictive ability. BMI, and other clinical criteria, do not appear to add to add further discrimination. The criteria identified are similar to the RCGP/NHS Diabetes Guidelines for Classification[13] which are based on consensus expert opinion. These guidelines would therefore, represent a suitable classification scheme until a stronger evidence base is available.

New studies are urgently needed to further develop and validate criteria suitable for classifying diabetes. We identified no studies in the Asian or pediatric populations, and only one study assessing features close to diagnosis[30]. Determining classification rules for both the incident and prevalent population would be important. Labelling a patient's diabetes at the outset is crucial as the classification given is rarely reconsidered. The evidence in this review should be used to redevelop a clinical prediction tool for Type 1 and Type 2 diabetes. Future studies should be large-scale, prospective, and give results for all racial and age groups using follow-up C-peptide measurements at least 3 years after diagnosis as an outcome. These studies would help answer if clinical criteria used in combination are sufficient to accurately classify diabetes, or whether investigations, such as islet autoantibodies, are needed in addition. Consideration of other forms of diabetes, such as monogenic diabetes, is also important.

We did not include antibodies in our search criteria as we limited our review to routinely available clinical criteria. Antibodies may represent a useful test at diagnosis, where C-peptide is of limited value due to the "honeymoon period", where patients with Type 1 diabetes are still able to produce significant amounts of their own insulin for a short period of time. A systematic review examining the use of antibodies at predicting long term insulin deficiency is presently in progress (Prospero reference CRD42012001736)

In conclusion, we have performed the first systematic review of the literature that examines using clinical criteria for the classification of diabetes. Although, only 11 studies were identified, age at diagnosis, and time to insulin were consistent as discriminatory criteria across studies. BMI did not aid classification over these factors. The discriminatory criteria identified were similar to those proposed by the RCGP/NHS Diabetes Classification guidelines, so these would represent a suitable classification scheme at present. New studies are urgently needed to assess and validate the most

appropriate clinical criteria. This review provides a summary of the current knowledge base for reference in any future studies developing classification rules.

**Declarations**:



Declaration of competing interests: All authors have completed the ICMJE uniform disclosure form at and declare: all authors had financial support from the National Institute for Health Research for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributorship: BS designed the review, carried out screening, reviewing, data extraction, quality assessment, and synthesis, and led writing of the manuscript. She is guarantor. JL helped design the review, carried out screening, reviewing, data extraction, quality assessment, and synthesis (independently, in parallel with BS), and helped draft and revise the manuscript. CC designed the search strategy and performed the initial literature search and revised the draft manuscript. JL performed additional searching, retrieved full text articles for review and revised the draft manuscript. BK and AJ helped design the review, and revised the draft manuscript. RP acted as third reviewer in cases of disagreement for the systematic review and revised the draft manuscript. CH

helped design the review, advised on synthesis, and revised the draft manuscript. AH helped design the review, advised on synthesis, and revised the draft manuscript.

Ethics approval was not required for this study as it was only a systematic review of the literature.

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Transparency: The lead author, BS, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: No additional data available

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**Figure 1**

Flow diagram showing inclusions and exclusions from title and abstract screening, and full text review. *Follow Up includes full texts identified from follow up of conference abstracts (n=29) and references identified from backwards and forwards citation chasing (n=14).

**Table 1. Criteria reported in the 11 included studies used to discriminate between C-peptide positive and negative patients.**

| First author (year) | Age Diag | Insulin treated or Time to insulin | BMI (or similar) | DKA | Onset (gradual or acute) |
|---|---|---|---|---|---|
| Prior 1991 | 1 | 2 | 3 | | |
| Welborn 1983 | 2 | 1 | 3 | | |
| Laakso 1987 | 3 | 1 | 2 | | |
| Benhamou 1992 | 1 | 2 | 3 | **x** | **x** |
| Shields 2010 | 1 | 2 | 3 | | |
| Service 1997 | # | # | # | # | # |
| Boyle 1999 | 1 | 2 | 3 | | |
| Welborn 1981 | 1 | 2 | | | |
| Nielsen 1986 | 1 | | | | |
| Ekpebegh 2013 | 1 | | 2 | Inc | |
| Balasubramanyam 2006 | | | 1 | Inc | |

Numbers indicate their ranking in terms of discriminatory ability within studies, with 1 representing the most discriminatory. # indicates used as part of an algorithm, but discriminatory value of individual criteria not reported. x indicates features not discriminatory. 'Inc' indicates inclusion criteria for the study, so feature could not be used to discriminate. Only features reported in more than one paper shown (see text for details of others).

**Table 2. Criteria for predicting Type 1 diabetes – single criteria**

| Cutoff | Author (year) | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| **i) Age at diagnosis (a/d)** | | | | | | | | | |
| <20 | Boyle 1999 | 3613 | 7 | 20 | 97 | 59 | 92 | 36 | 94 |
| **<=30** | **Prior 1991** | **575** | **61** | **84** | **82** | **83** | **83** | **88** | **77** |
| **<30** | **Nielsen 1986** | **215** | **69** | **64** | **88** | **76** | **72** | **92** | **53** |
| <30 | Ekpebegh | 71 | 49 | 57 | 72 | 65 | 65 | 67 | 63 |
| **<39** | **Shields 2010** | **72** | **56** | **68** | **97** | **83** | **81** | **96** | **70** |
| **<=40** | **Prior 1991** | **575** | **61** | **97** | **59** | **78** | **82** | **79** | **92** |
| **<=40** | **Welborn 1983** | **121** | **21** | **84** | **85** | **85** | **85** | **60** | **95** |
| **<=40** | **Welborn 1981** | **201** | **24** | **76** | **81** | **79** | **79** | **55** | **92** |
| <=40 | Laakso* 1987 | 171 | 67 | 61 | 79 | 70 | 67 | 85 | 44 |
| <45 | Boyle 1999 | 3613 | 7 | 65 | 57 | 61 | 57 | 10 | 96 |
| **ii) Insulin treatment/Time to insulin (tti) (a=all treatments, i=insulin treated only)** | | | | | | | | | |
| Cutoff | Author (year) | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
| on insulin (a) | Prior 1991 | 575 | 61 | 99 | 25 | 62 | 70 | 68 | 97 |
| **on insulin (a)** | **Welborn 1981** | **201** | **24** | **100** | **70** | **85** | **77** | **49** | **100** |
| **on insulin (a)** | **Boyle 1999** | **3613** | **7** | **91** | **61** | **76** | **63** | **15** | **99** |
| tti<=1.5m (i) | Shields 2010 | 72 | 56 | 80 | 56 | 68 | 69 | 70 | 69 |
| **tti<1y (a)** | **Prior 1991** | **575** | **61** | **92** | **75** | **84** | **85** | **85** | **85** |
| **tti<2y (a)** | **Welborn 1983** | **121** | **21** | **100** | **82** | **91** | **86** | **60** | **100** |
| **tti<=2y (i)** | **Laakso* 1987** | **90** | **67** | **70** | **86** | **78** | **75** | **91** | **58** |

**Table 2. Criteria for predicting Type 1 diabetes – single criteria (continued)**

| **iii) BMI** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cutoff | | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
| <20 | Boyle 1999 | 3613 | 7 | 10 | 98 | 54 | 92 | 33 | 94 |
| <25[†] | Prior 1991 | 575 | 61 | 34 | 92 | 63 | 57 | 87 | 47 |
| <25 | Boyle 1999 | 3613 | 7 | 41 | 86 | 64 | 83 | 18 | 95 |
| **<27[†]** | **Prior 1991** | **575** | **61** | **87** | **63** | **75** | **78** | **79** | **76** |
| **<=27[†]** | **Welborn 1983** | **121** | **21** | **80** | **67** | **74** | **69** | **38** | **93** |
| **<=27** | **Laakso* 1987** | **90** | **67** | **76** | **66** | **71** | **73** | **82** | **57** |
| **<28** | **Balasumbryaman 2006** | **294** | **60** | **67** | **86** | **77** | **78** | **79** | **77** |
| <29 | Boyle 1999 | 3613 | 7 | 71 | 57 | 64 | 58 | 11 | 96 |
| <29 | Shields 2010 | 72 | 56 | 78 | 56 | 67 | 68 | 69 | 67 |
| <30 | Ekpebegh | 71 | 49 | 77 | 47 | 62 | 62 | 59 | 68 |

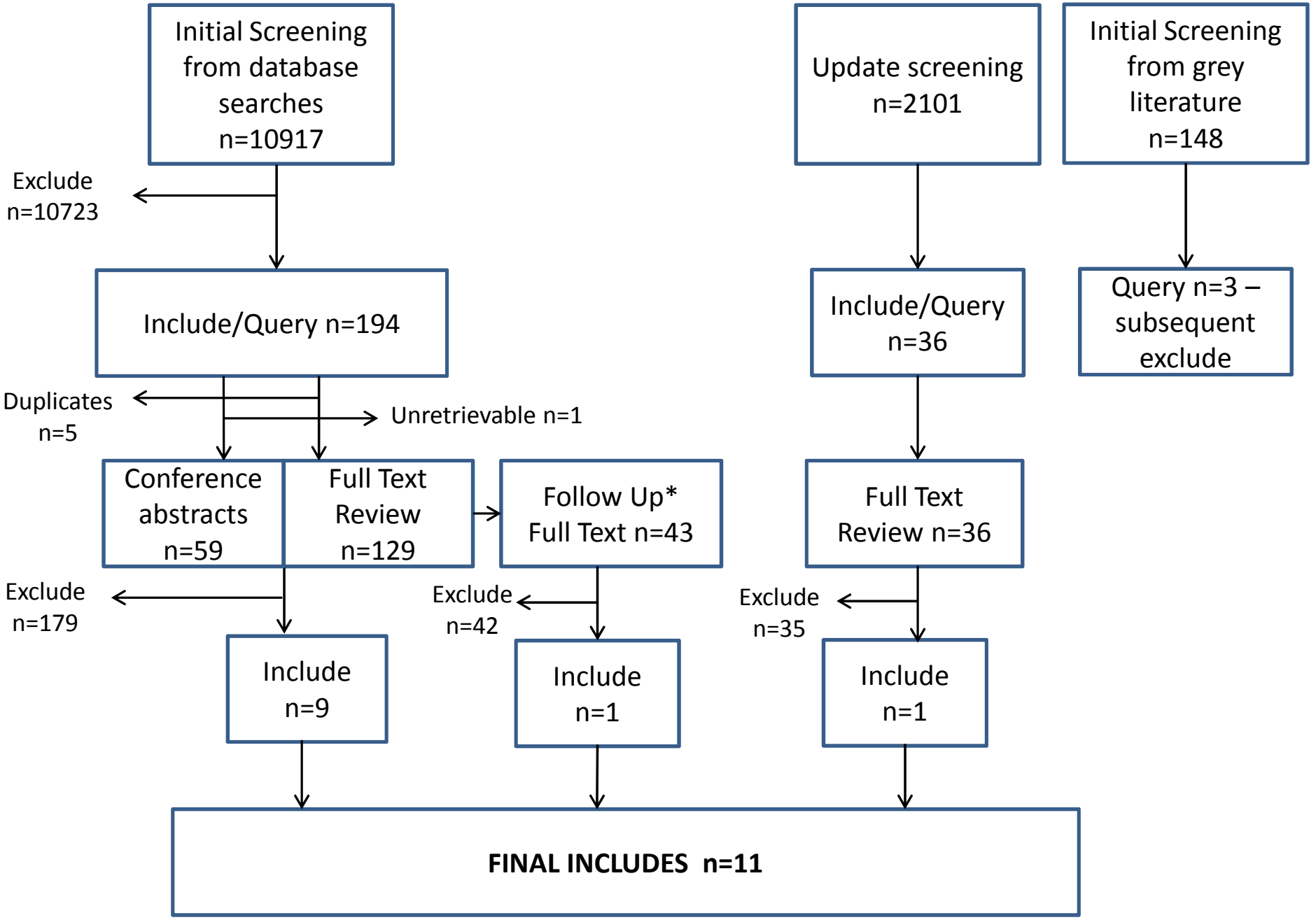
Sensitivity (sens), specificity (spec), proportion correctly classified (%correct), mean of sensitivity and specificity (mean sens & spec), positive predictive value (PPV), and negative predictive value (NPV) for i) age at diagnosis, ii) BMI, and iii) insulin treatment and/or time to insulin. Proportion of C-peptide negative patients (% C-pep neg) shown to aid interpretation of %correct, PPV and NPV. Criteria with a mean sensitivity and specificity >70% are highlighted in bold.

**male and female values combined, using postglucagon-stimulated results [†]converted from percentage desirable weight*

**Table 3** . Comparison of combinations of criteria over individual criteria. Data presented as overall percentage correctly classified according to C-peptide category (below or above cutoff for insulin deficiency) using cutoffs of individual criteria and combinations of criteria, for the 6 studies where comparison within studies was possible. Results in bold are those where the addition of another clinical feature provides better classification within studies, **p<0.01, ***p<0.001, by McNemar's test.

| | | Individual Criteria % correctly classified | | | Combined – 2 criteria % correctly classified | | | Combined – 3 criteria % correctly classified | |
|---|---|---|---|---|---|---|---|---|---|
| Author Year | N | Age at diagnosis | BMI (or equivalent) | Insulin treatment/ Time to insulin (TTI) | Age at diagnosis and BMI | Age at diagnosis and Insulin/TTI | BMI and Insulin/TTI | Age at diagnosis, BMI and Insulin/TTI | Regression equation or algorithm using all 3 criteria |
| Boyle | 3613 (1807[†]) | 92 | 58 | 63 | | 90 | | 93 | 93 |
| Laakso | 171 | 67 | 73 | 75 | 61 | 61 | 67 | 56 | |
| Prior | 575 | 82 | 78 | 85 | | **89*** ** | | 80 | 89 |
| Shields | 72 | 81 | 68 | 69 | | | | 82 | |
| Welborn 1981 | 203 | 79 | | 77 | | **88** ** | | | |
| Welborn 1983 | 121 | 85 | 69 | 86 | | **93** ** | | | 93 |

[†]regression equations/algorithms tested on a separate dataset, so a 2 sample chi-squared test is used to determine statistical significance


Initial Screening from database searches n=10917
Exclude n=10723
Include/Query n=194
Duplicates n=5
Unretrievable n=1
Conference abstracts n=59
Full Text Review n=129
Follow Up* Full Text n=43
Exclude n=179
Exclude n=42
Include n=9
Include n=1
Update screening n=2101
Include/Query n=36
Full Text Review n=36
Exclude n=35
Include n=1
Initial Screening from grey literature n=148
Query n=3 – subsequent exclude
FINAL INCLUDES n=11

# Online Supplemental Material

## Title: Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.

### Supplemental Methods

Quality Assessment

Quality assessment was based on QUADAS-2, the recommended approach for diagnostic accuracy studies, which considers risk of bias (internal validity) and applicability (external validity) in 4 domains: Patient Selection, Index Tests, Reference Standard and Patient Flow and Timing. Due to potential variations in the measurement of the Reference Standard, this was considered in more detail separately.

*Risk of bias:*
Risk of bias in terms of the way the study was conducted, was assessed by examining patient recruitment, the measurements of the clinical predictors, and recording any exclusions made. Timing of the predictors in relation to the C-peptide measurement was also assessed. Of particular interest was how the clinical criteria were derived.

*Applicability*
When determining external validity, the main point of interest was the inclusion/exclusion criteria, to assess whether the study in question matched our protocol and which subgroups of diabetes patients the study was applicable to. We also aimed to determine whether the clinical predictors (index tests) were applicable to our research question, particularly whether they could be replicated in clinical practice. The timing of these measurements and the reference standard was also of interest, as criteria at diagnosis is likely to differ to criteria measured later on in the course of a patient's diabetes.

*Reference standard*
When assessing the reference standard for insulin deficiency, details such as the sample taken, meal stimulus, and assay used for measurement were examined. C-peptide results were all converted to nmol/l (=0.333*ng/ml) and fasting serum equivalent[1] where necessary, to enable direct comparison. The justification for the cutoff for insulin deficiency was assessed.

### Supplemental Results

*Screening and full text review – further details*
Of 194 potential references, 59 studies were conference abstracts only and 5 were found to be further duplicates. Full texts were retrieved on 129 references. The remaining reference was unretrievable[2]. A further 29 references were identified from follow-up of conference abstracts, 6 of which had been published since the initial screening had been carried out, and full texts were retrieved on these. 11 studies were not in English. These were initially translated using google translate to gauge likely eligibility and in 10 cases it was clear the references were not appropriate. Full translation was required in only one case which appeared to have a table of relevance.

*Full text review - exclusions*
Of the 179 excluded studies at full text review stage, 146 were not diagnostic accuracy studies. 23 were excluded as the reference standard was incorrect (either not C-peptide or other features were incorporated into the reference standard along with C-peptide). 10 were excluded as the index test is not routinely measured (islet antibodies or HLA-alleles).

**Supplemental Table 1** – Summary data extracted from the 10 included papers.

| Author Year | Country | Year of study | Race of population | Sample size | Inclusion (I)/ Exclusion (E) | Treatments | Age group of pop'n | % Male | Prop'n with BMI below cutoff used | Prop'n C-peptide negative |
|---|---|---|---|---|---|---|---|---|---|---|
| Balasubramanyam 2006 | USA (Texas) | 1999-2003 | 44.8% African American; 43.5% Hispanic; 10.8% Caucasian; <1% Asian | 294 | I: Presented with DKA | Unclear – assume all treatments | | 60% | Cutoff of 28kg/$m^2$ = 44$^{th}$ centile | 40% |
| Benhamou 1992 | France | 1989-1990 | Not specified | 88 | I: End stage renal disease | All treatments | Not specified | ? | Unable to extract | 16% |
| Boyle 1999 | USA (Georgia) | 1991-1996 | All African American | 3613 (1807 for testing) | E: Serum creatinine >2mg/dl<br>E: Missing data | All treatments | Split by category – table 1 | 37% | 45% patients BMI≤29 | 7% |
| Ekpebegh 2013 | South Africa | 2010-2012 | Black African | 71 | I: Diagnosis of DKA | All treatments | Mean 34.7+/-15.3 | 54% | 65% BMI<30 | 49% |
| Laakso 1987 | Finland | 1987 | Not specified | 171 | I: Insulin treated only<br>I: aged 45-64 living in region of Kuopio central Hospital | Insulin treated only | Range 45-64 | 47% | 49% of patients BMI≤27 | 67% |
| Nielsen 1986 | Denmark | 1979-1980 | Not specified | 215 | I: Insulin treated only | Insulin treated Only | Not specified | 52% | - | 69% |
| Prior 1991 | USA (Baltimore) | 1980-1985 | 96.5% White | 575 | I: Mild-severe non-proliferative or early proliferative diabetic retinopathy; I: Aged 18-70 | All treatments | Range 18-70 | ? | 68% PDW<120%[a] | 61% |
| Service 1997 | USA (Rochester) | 1986 | Not specified | 346 | No specific exclusion criteria | All treatments | Not specified | ? | Unable to extract | 30% |
| Shields 2010 | UK | 2010 | Not specified | 72 | I: Insulin treated only<br>E: <5y duration and on insulin <2y of diagnosis | Insulin treated only | Adults | ? | 63% BMI<29 | 56% |
| Welborn 1981 | Australia | 1981 | Not specified | 201 | E: Known renal failure | All treatments | Mean 53 +/- 17 for hosp; 55 +/-16 for country | 53% | 43% of cohort PDW≤120%[a] | 24% |
| Welborn 1983 | Australia | 1983 | All Caucasian | 121 | No exclusions for food, glucose or renal status | Unclear – assume all | Adults | ? | Not specified | 21% |

[a]120% PDW (percentage desirable weight) equates to BMI<27.2 for men, <26.9 for women.

**Supplemental Table 2** - Quality Assessment of internal validity (risk of bias) and external validity (applicability of study) for included studies in terms of a) patient selection, b) the index tests and c) patient flow and timing. ✓ = low risk of bias/valid study, ? = risk of bias/validity unclear, ✗= high risk of bias/problems with validity

| **a) Patient Selection** | | | | |
|---|---|---|---|---|
| **Author Year** | **Internal Validity**<br>**Risk of bias in patient selection?** | | **External Validity**<br>**Does the study match our question?** | |
| Balasubramanyam 2006 | ✓ | Low. Consecutive recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides. | ✓ | Applicable only for those who have presented with DKA. |
| Benhamou 1992 | ✓ | Low. Random recruitment. Excluded secondary diabetes and missing data | ✓ | Applicable for ESRD patients only. Very few details of population |
| Boyle 1999 | ✓ | Low. New patients enrolled (random) – not all at diagnosis. Excluded renal disease and missing data | ✓ | Applicable for African American non renal disease group only |
| Ekpebegh 2013 | ? | Unclear – cross sectional but few details on recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides. | ✓ | Applicable only for those who have presented with DKA and Black African racial group. |
| Laakso 1986 | ✓ | Low. Random recruitment – 78% recruitment rate. | ✓ | Applicable for insulin treated patients only. Older patients |
| Nielsen 1986 | ✓ | Low. Consecutive recruitment. | ✓ | Applicable for insulin treated patients only. |
| Prior 1991 | ? | Unclear. 582/3711 with C-peptide measurements available. Possible selection bias as those with C-pep measured different from rest (diagnosed older, less likely to be insulin treated and slimmer) | ✓ | Applicable for patients with retinopathy only. 95% White. |
| Service 1997 | ✓ | Low. Cross-sectional survey. Representative of all diabetes 10-70 in Rochester area | ✓ | Applicable to Rochester population aged 10-70 |
| Shields 2010 | ✓ | Low. Recruited through retinal screening. Excluded non-insulin treated and short duration and long time to insulin. | ✓ | Applicable for insulin treated adults only. >5y duration; insulin treated within 2y of diagnosis |
| Welborn 1981 | ? | Unclear, likely random recruitment. Excluded renal failure | ✓ | Applicable for all except renal failure which was excluded in hospital clinic patients. |
| Welborn 1983 | ? | Unclear. Possibly some of same patients as other Welborn paper | ? | Unclear |

| **b) Index Test (Clinical Predictors)** | | | | |
|---|---|---|---|---|
| **Author** | **Internal Validity**<br>**Is there a risk of bias in the way the index tests were measured/cutoffs derived?** | | **External Validity**<br>**Are the measurements applicable for our question?** | |
| Balasubramanyam 2006 | ✓ | Low. Prespecified – objective measures | ✓ | BMI applicable – assume taken close to DKA episode. |

| | | | | |
|---|---|---|---|---|
| Benhamou 1992 | × | High. Regression equation internally derived. Mix of self report/questionnaire – possible recall bias. Unclear how BMI measured | × | Maximum BMI difficult to replicate as dependent on how many and when repeat measurements are taken. |
| Boyle 1999 | ✓ | Low. Systematic assessment – height and weight measured (ref 21). Clinical rules CRI and CRII prespecified. Others not defined but split validation used. | ✓ | Yes – BMI cutoff results applicable to African American population. |
| Ekpebegh 2013 | ? | Unclear for age at diagnosis. Low for BMI - Systematic assessment and cutoffs defined in advance. | ✓ | Yes. |
| Laakso 1986 | ? | Unclear. Assumed taken off register so unlikely recall bias. Unclear when BMI measured. Lack of detail | ✓ | Yes. |
| Nielsen 1986 | ? | Unclear. Little detail on how cutoffs derived. | ✓ | Yes. |
| Prior 1991 | ✓ | Low. Clinical rules pre-specified | ✓ | Yes |
| Service 1997 | ✓ | Low. Algorithm pre-specified based on NDDG guidelines. | ? | |
| Shields 2010 | × | High – cutoffs internally derived. Age at diagnosis, BMI and time to insulin all self reported – possible recall bias | ? | Unclear. BMI taken at time of study so may not be valid at other time points |
| Welborn 1981 | ? | Unclear how criteria chosen.<br>Height and weight measured, but no details on how age at diagnosis and treatment were recorded – potential recall bias if patient reported. | ✓ | Yes. |
| Welborn 1983 | ? | Unclear. No details of how key criteria obtained. | ✓ | Unclear. Very little detail, but similar study to Welborn 1981; possible overlap. |

| **c) Patient Flow and Timing** | | | | |
|---|---|---|---|---|
| **Author** | **Internal Validity**<br>**Could exclusions have introduced bias?** | | **External Validity**<br>**Are the timings in the study applicable to our question?** | |
| Balasubramanyam 2006 | ? | Unclear. Doesn't state numbers due to missing data | ✓ | Applicable to first 12 months following DKA episode (not necessarily at diagnosis of diabetes). |
| Benhamou 1992 | ✓ | Low. C-peptide measured on random selection of patients | ? | Unclear. Cross sectional. Duration of diabetes not reported. |
| Boyle 1999 | ✓ | Low. Measures taken at time of enrolment. | ? | Median diabetes duration 1y but variability around that. |
| Ekpebegh 2013 | ✓ | Unclear . No exclusions reported. | ✓ | Applicable to cases presenting with DKA, first manifestation of diabetes. |
| Laakso 1986 | ? | Unclear. No exclusions reported. | ? | Cross-sectional. Unclear when measured in relation to C-peptide. |
| Nielsen 1986 | ? | Unclear. Small subset with C-peptide | ? | Cross-sectional. Don't know when baseline visit is in relation to diabetes duration. |
| Prior 1991 | ? | Unclear. 346/381 with C-peptide measured. Not clear why | ? | Cross sectional. Don't know when visit is in terms |

| | | | | |
|---|---|---|---|---|
| | | some missing, but low numbers. | | of duration of disease |
| Service 1997 | ✓ | Low. 11 deaths and 1 refusal – potentially lost those with lower C-peptide but small numbers. | ✓ | Yes. Some data split by duration. |
| Shields 2010 | ✓ | Low. C-peptide measures were not included for 46 patients in analysis as either <3h post-food or abnormal renal function. Better for reference standard; timing of sample unlikely to be a bias of people entering the study. | ? | Unclear. Duration of diabetes not reported so cannot determine when results would be applicable in time course of diabetes. |
| Welborn 1981 | ? | Unclear. Likely similar to above, as same authors and similar study. | ? | Unclear |

**Supplemental Table 3.** Reference standard C-peptide cutoffs for insulin deficiency. Cutoffs ordered from lowest to highest. Data presented for each study: cutoff as originally described, cutoff converted to nmol/l, fasting serum equivalent[a] to allow direct comparison across studies, assessment of the justification of the cutoff for insulin deficiency, and its applicability. For studies that reported two cutoffs, the most discriminatory is presented.

| Author of study | Cutoff for insulin deficiency in original units; sample type; stimulus used | Cutoff converted to nmol/l, fasting serum[a] | How was cutoff chosen? | Cutoff applicable? |
|---|---|---|---|---|
| Prior 1993 | 80 pmol/l; plasma; post-sustacal | 0.03 nmol/l | Unclear. ?chosen to maximise clinical diffs. | Yes, but likely to be internally derived. Very few patients between 0.04 and 0.32 nmol/l so any cutoff in this range would have led to similar results. |
| Welborn 1983 | 0.16 nmol/l; blood (plasma?); random | 0.06 nmol/l | References Welborn 1981 | Yes, although cutoff described based on fasting samples, whereas in this study samples were taken without reference to food ingestion. |
| Ekpebegh 2013 | 0.5 ng/mL; serum; stimulated | 0.07 nmol/l | Not specified. | Unclear - consistent with other studies, but patients recruited close to diagnosis so C-peptide may be affected by “honeymoon" period. |
| Shields 2010 | 0.2 nmol/mmol; urine C-peptide creatinine ratio; post-meal | 0.08 nmol/l | As reported by Besser et al[3]. to discriminate Type 1 diabetes from MODY. | Yes. |
| Service 1997 | 0.17 pmol/ml; blood (plasma?); fasting (and post-glucagon increment <0.07[b]) | 0.17 nmol/l | “Arbitrarily segregated” … “using previously published criteria for the characterization of IDDM and NIDDM”. No reference provided | Unclear from paper but consistent with Welborn 1981. Results at different cutoffs for fasting and increment are also presented. |
| Welborn 1981 | 0.16 nmol/l; serum; fasting | 0.16 nmol/l | <0.16 well outside 2SDs of mean and exclusively identifies those on insulin therapy. | Yes, but internally derived - insulin use possibly used to determine the reference standard. |
| Benhamou 1992 | 0.6 ng/ml; plasma; fasting | 0.2 nmol/l | DCCT[4] – No IDDM patients had fasting C-peptide >0.6ng/ml 5 years after diagnosis | Yes. |
| Nielsen 1986 | 0.20 pmol/ml; plasma; fasting | 0.2 nmol/l | Reference Madsbad et al[5]. from discriminating insulin from non-insulin treated patients | Yes. |
| Laakso 1987 | 0.60 nmol/l; blood; post-glucagon | 0.2 nmol/l | Not specified. | Unclear, but consistent with other studies. |
| Balasumbryaman 2006 | 1 ng/ml; serum; fasting OR 1.5 ng/ml; serum; post-glucagon | 0.3 nmol/l OR 0.2 nmol/l | Referenced Maldonado et al[6]. where cutoff obtained from ROC analysis in a “relevant population” | Yes. |
| Boyle 1999 | 0.9 ng/ml; not specified (likely plasma); fasting | 0.3 nmol/l | Shows histogram and references 6 papers (although 0.9 ng/ml not used as a cutoff in these papers) | Unclear but consistent with other cutoffs reported. |

[a]All converted to nmol/l (=0.333*ng/ml); urine to serum, and stimulated to fasting C-peptide (fasting=stimulated/2.5 formula unpublished but derived from MMTT data[78]; 0.2nmol/mmol UCPCR=0.2nmol/l stimulated serum C-peptide as described in the review by Jones et al[1]). [b]More than one cutoff reported in the paper.

**Supplemental Tables 4**. Two-by-two tables of clinical criteria cutoffs against reference standard C-peptide cutoffs for insulin deficency. Data extracted either directly as reported in the paper, or indirectly using reported estimates of sensitivity/specificity or positive/negative predictive value, and sample size and proportion of C-peptide negative/positive. C-peptide negative and C-peptide positive are determined as values below or above the cutoff for insulin deficiency reported in the paper.

**Single criteria:**

Balasumbryaman 2006

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <28kg/m$^1$** | 142 | 42 | 184 |
| **BMI>=28kg/m$^2$** | 23 | 86 | 109 |
| | 165 | 128 | 293* |

*1 result missing

Boyle 1999

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20y** | 50 | 88 | 138 |
| **Age at diagnosis >=20y** | 195 | 3280 | 3475 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <45y** | 160 | 1455 | 1615 |
| **Age at diagnosis >=45y** | 85 | 1913 | 1998 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <20 kg/m$^2$** | 25 | 51 | 76 |
| **BMI>=20 kg/m$^2$** | 220 | 3317 | 3537 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<25 kg/m$^2$** | 100 | 462 | 562 |
| **BMI>=25 kg/m$^2$** | 145 | 2906 | 3051 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <29 kg/m$^2$** | 175 | 1463 | 1638 |
| **BMI>=30 kg/m$^2$** | 70 | 1905 | 1975 |
| | 245 | 3368 | 3613 |

Ekpebegh 2013

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <30y** | 20 | 10 | 30 |
| **Age at diagnosis >=30y** | 15 | 26 | 41 |
| | 35 | 36 | 71 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<30kg/m$^2$** | 27 | 19 | 46 |
| **BMI>=30kg/m$^2$** | 8 | 17 | 25 |
| | 35 | 36 | 71 |

Laakso 198
using postglucagon male and female combined as the most discriminative

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 70 | 12 | 82 |
| **Age at diagnosis >40y** | 45 | 44 | 89 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=2y** | 80 | 8 | 88 |
| **Time to insulin >2y** | 35 | 48 | 83 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<=27kg/m$^2$** | 87 | 19 | 106 |
| **BMI >27kg/m$^2$** | 28 | 37 | 65 |
| | 115 | 56 | 171 |

Nielsen 1986

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30y** | 95 | 8 | 103 |
| **Age at diagnosis >30y** | 53 | 59 | 112 |
| | 148 | 67 | 215 |

Prior 1991

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30y** | 295 | 40 | 335 |
| **Age at diagnosis >30y** | 56 | 184 | 240 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 340 | 91 | 431 |
| **Age at diagnosis >40y** | 11 | 133 | 144 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **PDW<100%** | 118 | 17 | 135 |
| **PDW>=100%** | 233 | 207 | 440 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **PDW<120%** | 306 | 83 | 389 |
| **PDW>120%** | 45 | 141 | 186 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **On insulin** | 349 | 168 | 517 |
| **Off insulin** | 2 | 56 | 58 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <1y** | 322 | 56 | 378 |
| **Time to insulin >=1y** | 29 | 168 | 197 |
| | 351 | 224 | 575 |

Shields 2010

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <39y** | 27 | 1 | 28 |
| **Age at diagnosis >=39y** | 13 | 31 | 44 |
| | 40 | 32 | 72 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <29kg/m$^2$** | 31 | 14 | 45 |
| **BMI>=29kg/m$^2$** | 9 | 18 | 27 |
| | 40 | 32 | 72 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=1.5m** | 32 | 14 | 46 |
| **Time to insulin >1.5m** | 8 | 18 | 26 |
| | 40 | 32 | 72 |

Welborn 1983

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| | | | |

| | | | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 21 | 14 | 35 |
| **Age at diagnosis >40y** | 4 | 82 | 86 |
| | 25 | 96 | 121 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **PDW<=120%** | 20 | 32 | 52 |
| **PDW>120%** | 5 | 64 | 69 |
| | 25 | 96 | 121 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **Time to insulin <2y** | 25 | 17 | 42 |
| **Time to insulin >2y + not on insulin** | 0 | 79 | 79 |
| | 25 | 96 | 121 |

Welborn 1981

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 35 | 29 | 64 |
| **Age at diagnosis >40** | 11 | 126 | 139 |
| | 46* | 155 | 203 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **On insulin** | 48 | 47 | 95 |
| **Off insulin** | 0 | 108 | 108 |
| | 48 | 155 | 203 |

**Combined criteria**

Boyle 1999

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 and insulin treated** | 33 | 104 | 137 |
| **Other** | 74 | 1596 | 1670 |
| | 107 | 1700 | 1807 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 insulin treated and BMI <26** | 16 | 27 | 43 |
| **Other** | 91 | 1673 | 1764 |
| | 107 | 1700 | 1807 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <28.9 insulin treated and BMI <31.7** | 26 | 49 | 75 |
| **Other** | 81 | 1651 | 1732 |
| | 107 | 1700 | 1807 |

Laakso 1987

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 and time to insulin <=2y** | 51 | 2 | 53 |
| **Opposite** | 64 | 54 | 118 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 and BMI <=27** | 53 | 5 | 58 |
| **Opposite** | 62 | 51 | 113 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=2y and and BMI <=27** | 63 | 4 | 67 |
| **Opposite** | 52 | 52 | 104 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 , time to insulin <=2y and and BMI <=27** | 40 | 1 | 41 |
| **Opposite** | 75 | 55 | 130 |
| | 115 | 56 | 171 |

Prior 1991

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30, time to insulin <=1y and PDW<120%** | 248 | 11 | 259 |
| **Opposite** | 103 | 213 | 316 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30, time to insulin <=1y OR ad<40, tti<1y PDW<120%** | 309 | 22 | 331 |
| **Opposite** | 42 | 202 | 244 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20, time to insulin immediately** | 238 | 16 | 254 |
| **Other** | 113 | 208 | 321 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20, time to insulin immediately OR Age at diagnosis >=20, time to insulin immediately PDW<=120%** | 328 | 61 | 389 |
| **Other** | 23 | 163 | 186 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 tti <1y** | 277 | 15 | 292 |
| **Other** | 74 | 209 | 283 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <40 tti <1y** | 313 | 28 | 341 |
| **Other** | 38 | 196 | 234 |
| | 351 | 224 | 575 |

Welborn 1983

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <40 and tti<=2y** | 21 | 4 | 25 |
| **Other** | 4 | 92 | 96 |
| | 25 | 96 | 121 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <=40y tti<2y OR age diag>40y tti<2y and PDW<120%** | 23 | 6 | 29 |
| **Other** | 2 | 90 | 92 |

| | | | |
|---|---|---|---|
| | 25 | 96 | 121 |

Welborn 1981

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag<=4-y and on insulin** | 35 | 12 | 47 |
| **Other** | 13 | 143 | 156 |
| | 48 | 155 | 203 |

**Equations or algorithms**

Service 1997

Algorithm:
Type 1=insulin treated+ketosis+slim OR insulin treated, no ketosis, diagnosed <=21y and acute onset

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Type 1 acc to algorithm** | 74 | 25 | 99 |
| **Other** | 10 | 237 | 247 |
| | 84 | 262 | 346 |

Benhamou 1992

Regression equation = T=(0.01166*time to insulin)+(0.01324*age diagnosis)+(0.01188*BMI max)-0.22834.

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **T<=0.5** | 14 | 3 | 17 |
| **T>0.5** | 0 | 71 | 71 |
| | 14 | 74 | 88 |

Boyle 1999

Regression equation =
Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI)

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **T1 prob>0.2** | 55 | 153 | 208 |
| **T1 prob<=0.2** | 52 | 1547 | 1599 |
| | 107 | 1700 | 1807 |

**Supplemental Table 5 Criteria for predicting insulin deficiency – combined criteria**

| Age at diagnosis (a/d) and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| a/d<=40 BMI<=27 | Laakso 1987 | 46 | 91 | 61 | 91 | 45 | 67 |

| Time to insulin (tti) and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| tti<=2 BMI<=27 | Laakso 1987 | 55 | 93 | 67 | 94 | 50 | 67 |

| Age at diagnosis and time to insulin | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **a/d<=20 tti immed** | **Prior 1991** | **68** | **93** | **78** | **94** | **65** | **61** |
| **a/d<30 tti<1y** | **Prior 1991** | **79** | **93** | **85** | **95** | **74** | **61** |
| ad<30 on insulin | Boyle 1999 | 31 | 94 | 90 | 76 | 96 | 7 |
| **ad <=40 on insulin** | **Welborn 1981** | **73** | **92** | **88** | **74** | **92** | **24** |
| **a/d<40 tti<1y** | **Prior 1991** | **89** | **88** | **89** | **92** | **84** | **61** |
| **ad<=40 tti<=2** | **Welborn 1983** | **84** | **96** | **93** | **84** | **96** | **21** |
| a/d<=40 tti<=2 | Laakso 1987 | 44 | 96 | 61 | 96 | 46 | 67 |

| Age at diagnosis, tti and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **a/d<20 tti immed OR a/d>=20 ins immed PDW<=120** | **Prior 1991** | **93** | **73** | **85** | **84** | **88** | **61** |
| ad<28.9 on ins bmi<31.7 | Boyle 1999 | 24 | 97 | 93 | 35 | 95 | 7 |
| **a/d<30 tti<1y PDW<120%** | **Prior 1991** | **71** | **95** | **80** | **96** | **67** | **61** |
| **a/d<30 tti<1 OR a/d<40 tti<1 PDW<120%** | **Prior 1991** | **88** | **90** | **91** | **93** | **83** | **61** |
| ad<30 on ins BMI<26 | Boyle 1999 | 15 | 98 | 93 | 37 | 95 | 7 |
| a/d<=40 tti<=2 BMI<=27 | Laakso 1987 | 35 | 98 | 56 | 98 | 42 | 67 |
| **ad<=40 tti<2 OR ad>40 tti<2 PDW<120%** | **Welborn 1983** | **92** | **94** | **93** | **79** | **98** | **21** |

| Equations or algorithms | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **Algorithm: Ins treated & ketosis & ≤120%PDW OR** | **Service 1997** | **75** | **96** | **90** | **88** | **90** | **24** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Ins treated & no ketosis & age diag<21y & acute onset** | | | | | | | |
| **Regression equation (T1 if >0.5): (0.0116*tti)+(0.01324*age diag)+(0.01188*BMI)** | **Benhamou 1992** | **100** | **96** | **97** | **82** | **100** | **16** |
| Regression equation (T1=prob>0.2) Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI) | Boyle 1999 | 51 | 91 | 89 | 26 | 97 | 7 |
| Classification tree: Insulin treated, diagnosed<28.9 and BMI<31.7 | Boyle 1999 | 24 | 97 | 93 | 35 | 95 | 7 |
| Classification tree including age diag, tti and BMI: *Details not reported* | Shields 2010 | | | 82 | | | |

**Supplemental Search Annex**

| Database | Hits |
|---|---|
| 1. MEDLINE | 5804 |
| 2. MEDLINE in Process | 205 |
| 3. EMBASE | 8566 |
| 4. PsycINFO | 23 |
| 5. Social Policy and Practice | 0 |
| 6. AMED | 11 |
| 7. British Nursing Index (BNI) | 11 |
| 8. CINAHL | 24 |
| 9. HMIC | 5 |
| 10. Sociological Abstracts | 3 |
| 11. ASSIA | 2 |
| 12. Cochrane (all) | 1611 (1613 2 from methods) |
| 13. Web of Science (Conference Proceedings Citation Index) | 4792 |
| 14. Centre for Reviews and Dissemination | 3 |
| Total | 21060 |
| Duplicates Removed | -10143 |
| Unique Records | 10917 |

1.
**Database:** MEDLINE
**Host:** OVID
**Data Parameters:** 1946 to October Week 2 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 5804
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 57591 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 29301 |
| 3 | (T1DM or dm1).ti,ab. | 2338 |
| 4 | diabet$.ti,ab. | 348751 |
| 5 | 1 or 2 or 3 or 4 | 355909 |
| 6 | C-Peptide/ | 6951 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 8707 |
| 8 | "Connecting Peptide$".ti,ab. | 292 |
| 9 | 6 or 7 or 8 | 11014 |
| 10 | 5 and 9 | 6230 |
| 11 | exp animals/ not humans.sh. | 3795620 |
| 12 | 10 not 11 | 5897 |

| | | |
|---|---|---|
| 13 | limit 12 to yr="1979 -Current" | 5804 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** Medline Endnote RIS n=5804.txt

2.
**Database:** Medline in Process
**Host:** OVID
**Data Parameters:** October 22nd , 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits: 205**
**Strategy:**

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 1502 |
| 3 | (T1DM or dm1).ti,ab. | 222 |
| 4 | diabet$.ti,ab. | 17913 |
| 5 | 1 or 2 or 3 or 4 | 17961 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 285 |
| 8 | "Connecting Peptide$".ti,ab. | 8 |
| 9 | 6 or 7 or 8 | 291 |
| 10 | 5 and 9 | 205 |
| 11 | exp animals/ not humans.sh. | 3 |
| 12 | 10 not 11 | 205 |
| 13 | limit 12 to yr="1979 -Current" | 205 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** Medline in Process RIS n=205.txt

**3.**
**Database:** Embase
**Host:** OVID
**Data Parameters:** Embase 1980 to 2012 Week 42, Embase 1974 to 1979
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 8566
**Strategy:**

Search Strategy:

| # | Searches | Results |
|---|---|---|

| | | |
|---|---|---|
| 1 | insulin dependent diabetes mellitus/ | 70536 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 41404 |
| 3 | (T1DM or dm1).ti,ab. | 4248 |
| 4 | diabet$.ti,ab. | 495933 |
| 5 | 1 or 2 or 3 or 4 | 507285 |
| 6 | C peptide/ | 11467 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 11576 |
| 8 | "Connecting Peptide$".ti,ab. | 307 |
| 9 | 6 or 7 or 8 | 14807 |
| 10 | 5 and 9 | 8775 |
| 11 | exp animal/ not human/ | 1352023 |
| 12 | 10 not 11 | 8718 |
| 13 | limit 12 to yr="1979 -Current" | 8566 |

**Limits:** The search is limited to human only populations and by date to 1979-Current.
**Notes:** N/A
**File Name:** Embase Endnote RIS n=8566.txt

**4.**
**Database:** PsycINFO
**Host:** OVID
**Data Parameters:** 1806 to October Week 3 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 23
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 1197 |
| 3 | (T1DM or dm1).ti,ab. | 178 |
| 4 | diabet$.ti,ab. | 16010 |
| 5 | 1 or 2 or 3 or 4 | 16087 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 70 |
| 8 | "Connecting Peptide$".ti,ab. | 1 |
| 9 | 6 or 7 or 8 | 71 |
| 10 | 5 and 9 | 25 |
| 11 | exp animals/ not humans.sh. | 250508 |
| 12 | 10 not 11 | 23 |

| | | |
|---|---|---|
| 13 | limit 12 to yr="1979 -Current" | 23 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** PsycINFO Endnote RIS n=23.txt

**5.**
**Database:** Social Policy and Practice (SPP)
**Host:** OVID
**Data Parameters:** 201207
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 0
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 59 |
| 3 | (T1DM or dm1).ti,ab. | 0 |
| 4 | diabet$.ti,ab. | 839 |
| 5 | 1 or 2 or 3 or 4 | 839 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 0 |
| 8 | "Connecting Peptide$".ti,ab. | 0 |
| 9 | 6 or 7 or 8 | 0 |
| 10 | 5 and 9 | 0 |
| 11 | exp animals/ not humans.sh. | 0 |
| 12 | 10 not 11 | 0 |
| 13 | limit 12 to yr="1979 -Current" | 0 |

**Limits:** N/A
**Notes:** N/A
**File Name:** No File Recorded

6.
**Database:** AMED
**Host:** Ebsco Host
**Data Parameters:** 1995-Current
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 11
**Strategy:**

TI diabet* OR AB diabet*
TI ( ((c-peptide*) or (c peptide*)) ) OR AB ( ((c-peptide*) or (c peptide*)) )
TI "Connecting Peptide*" OR AB "Connecting Peptide*"
S2 or S3
(S2 or S3) AND (S1 and S4)

**Limits:** None Used

**Notes:** N/A
**File Name:** Amed Endnote RIS n=11.txt

7.
**Database:** British Nursing Index (BNI)
**Host:** ProQuest
**Data Parameters:** 1994-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 11
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A
**File Name:** BNI Endnote RIS n=11

8.
**Database:** Cinahl
**Host:** Ebsco Host
**Data Parameters:** 1981-Current
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 24
**Strategy:**

TI diabet* OR AB diabet*
Search modes - Boolean/Phrase

TI ( (("c peptide*") or (c-peptide*) or (connecting peptide*)) ) OR AB ( (("c peptide*") or (c-peptide*) or (connecting peptide*)) )
Search modes - Boolean/Phrase

S1 and S2
Search modes - Boolean/Phrase

S1 and S2
Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase

**Limits:** N/A
**Notes:** A server-side de-duplication was run to exclude Medline records.
**File Name:** Cinahl Endnote RIS n=24.txt

9.
**Database:** HMIC
**Host:** OVID
**Data Parameters:** 1979 to September 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 5
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |

| | | |
|---|---|---|
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 132 |
| 3 | (T1DM or dm1).ti,ab. | 3 |
| 4 | diabet$.ti,ab. | 3553 |
| 5 | 1 or 2 or 3 or 4 | 3553 |
| 6 | C peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 10 |
| 8 | "Connecting Peptide$".ti,ab. | 0 |
| 9 | 6 or 7 or 8 | 10 |
| 10 | 5 and 9 | 5 |
| 11 | exp animal/ not human/ | 0 |
| 12 | 10 not 11 | 5 |
| 13 | limit 12 to yr="1979 -Current" | 5 |

**Limits:** Date limited 1979-Current
**Notes:** N/A
**File Name:** HMIC Endnote RIS n=5.txt

10.
**Database:** Sociological Abstracts
**Host:** ProQuest
**Data Parameters:** 1963-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 3
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A
**File Name:** Soc Abs Endnote RIS n=3

11
**Database:** ASSIA
**Host:** ProQuest
**Data Parameters:** 1987-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 2
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A

**File Name:** Assia Endnote RIS N=2

12.
**Database:** Cochrane Library
**Host:** http://www.thecochranelibrary.com/view/0/index.html
**Data Parameters:** Issue 10 of 12, Oct 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 1611 (Reviews: 127; DARE: 20; Central 1449; HTA 3; NHS EEDS 12)
**Strategy:**

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#2 ((typ* 1 or typ* I or type 1) near/3 diabet*)
#3 (T1DM or dm1)
#4 diabet*
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [C-Peptide] explode all trees
#7 ((c-peptide*) or (c peptide*))
#8 "Connecting Peptide*"
#9 #6 or #7 or #8
#10 #5 and #9

**Limits:** N/A
**Notes:** N/A
**File Name:**

13.
**Database:** Web of Science
**Host:** ISI
**Data Parameters:** 1900-Present. SSCI, 1975-Present
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 4792
**Strategy:**

Topic=(diabet*) AND Topic=((("c peptide*") or ("c-peptide*") or ("connecting peptide*")))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1979-01-01 - 2012-10-23
Lemmatization=Off

**Limits:** Lemmatization=Off. The search was limited by date 1979-Current
**Notes:** SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH were all searched
**File Name:** WOS Endnote RIS n=4792

14.
**Database:** CRD
**Host:** http://www.york.ac.uk/inst/crd/index.htm
**Data Parameters:** 1989-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 3
**Strategy:**

**(diabet*) AND ((("c peptide*") or (c-peptide*) or (connecting peptide*))) FROM 1979 TO 2012**

**Limits:** Date Limited 1979-2012
**Notes:** N/A
**File Name:** CRD endnote RIS n=3.txt

15.
**Database:** PROSPERO
**Host:** http://www.york.ac.uk/inst/crd/index.htm

**Data Parameters:** Feb 2011-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 1
**Strategy:**

**(C peptide)**

**Limits:** N/A
**Notes:** N/A
**File Name:** Prospero

**Supplementary References**

1. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013;**30**(7):803-17 doi: 10.1111/dme.12159[published Online First: Epub Date]|.
2. Cisse A, Chevenne D, Chauffert M, et al. [Contribution of plasma C-peptide to the classification of sugar diabetes in Dakar, Senegal]. Dakar medical 1997;**42**(1):11-4
3. Besser RE, Shepherd MH, McDonald TJ, et al. Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-{alpha}/hepatocyte nuclear factor 4-{alpha} maturity-onset diabetes of the young from long-duration type 1 diabetes. Diabetes Care 2011;**34**(2):286-91 doi: 10.2337/dc10-1293[published Online First: Epub Date]|.
4. Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). The DCCT Research Group. The Journal of clinical endocrinology and metabolism 1987;**65**(1):30-6 doi: 10.1210/jcem-65-1-30[published Online First: Epub Date]|.
5. Madsbad S, Faber OK, Binder C, et al. Prevalence of residual beta-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. Diabetes 1978;**27 Suppl 1**:262-4
6. Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. The Journal of clinical endocrinology and metabolism 2003;**88**(11):5090-8 doi: 10.1210/jc.2003-030180[published Online First: Epub Date]|.
7. Besser RE, Ludvigsson J, Jones AG, et al. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care 2011;**34**(3):607-9 doi: 10.2337/dc10-2114[published Online First: Epub Date]|.
8. Jones AG, Besser RE, McDonald TJ, et al. Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabet Med 2011;**28**(9):1034-8 doi: 10.1111/j.1464-5491.2011.03272.x[published Online First: Epub Date]|.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supp |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7/Supp p1 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 1<br>7 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8/Fig 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Supp Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supp Table 2 & 3 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 10/Table 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 18 |

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

BMJ Open

# Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.



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| Secondary Subject Heading: | Evidence based practice |
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| | |

**Title: Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.**

**Short title:** Clinical criteria for Type 1 & Type 2 diabetes

Authors: Beverley M Shields[1] PhD, Jaime L Peters[2] PhD, Chris Cooper[2] MA, Jenny Lowe[2], Bridget A Knight[1,3] PhD, Roy J Powell[3] PhD, Angus Jones[1] PhD, Christopher J Hyde[2] MD, Andrew T Hattersley[1] DM

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Key words: diabetes, classification, Type 1, Type 2, systematic review

Word count: 3598. 3 Tables, 1 figure + Supplementary material.

**Abstract: (297 words).**

Objective: Clinicians predominantly use clinical features to differentiate Type 1 from Type 2 diabetes yet there are no evidence-based clinical criteria to aid classification of patients. Misclassification of diabetes is widespread (7-15% of cases), resulting in patients receiving inappropriate treatment. We sought to identify which clinical criteria could be used to discriminate Type 1 and Type 2 diabetes.

Design: Systematic review of all diagnostic accuracy studies published since 1979 using clinical criteria to predict insulin deficiency (measured by C-peptide).

Data sources: 14 databases including: MEDLINE, MEDLINE in Process and EMBAaSE. The search strategy took the form of: (terms for diabetes) AND (terms for C-Peptide).

Eligibility criteria: Diagnostic accuracy studies of any routinely available clinical predictors against a reference standard of insulin deficiency defined by cutoffs of C-peptide concentrations. No restrictions on race, age, language, or country of origin.

Results: 10,917 abstracts were screened, and 231 full texts reviewed. 11 studies met inclusion criteria, but varied by age, race, year, and proportion of participants who were C-peptide negative. Age at diagnosis was the most discriminatory feature in 7/9 studies where it was assessed, with optimal cutoffs (>70% mean sensitivity and specificity) across studies being <30y or <40y. Use of/time to insulin treatment and BMI were also discriminatory. When combining features, BMI added little over age at diagnosis and/or time to insulin (<1% improvement in classification).

Conclusions: Despite finding only 11 studies, and considerable heterogeneity between studies, 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. The criteria identified are similar to the RCGP/NHS Diabetes classification guidelines, which use age at diagnosis <35y and time to insulin <6m. Until further studies are carried out, these guidelines represent a suitable classification scheme.

Systematic Review Registration: PROSPERO reference CRD42012001736

**Article summary**

**Strengths and limitations of this study:**

*Strengths:*

- We have carried out a comprehensive and robust systematic review in accordance with PRISMA guidelines and our initial published protocol.
- We screened a large number of literature sources, and all reviewing and data extraction was carried out in duplicate independently by two authors (BS and JP).

*Limitations:*

- Considerable heterogeneity across studies precluded a formal meta-analysis
- A limited number of studies were found meaning there is still considerable uncertainty around criteria for classification of Type 1 and Type 2 diabetes
- Variability in the reference standard of insulin deficiency across studies also led to further uncertainty around findings limiting direct usefulness of criteria

**Background:**

Correct classification of a patient's diabetes is crucial for ensuring they receive the most appropriate treatment and management. Current guidelines for the treatment of diabetes are specific to Type 1 and Type 2 diabetes and these show marked differences[1-4], reflecting the difference in endogenous insulin production between the two subtypes. Patients with Type 1 diabetes rapidly develop severe insulin deficiency, leading to high glycemic instability, and so require accurate insulin replacement (such as multiple injections and carbohydrate counting), and have poor response to non insulin therapies[3 5]. Patients with Type 2 diabetes still continue to produce substantial amounts of their own insulin, and, therefore, respond to non insulin therapy, have more stable glycemia and, if insulin treatment is needed, may achieve good control with non-physiological insulin regimes[6 7].

Currently, there are no published, evidence based, guidelines or criteria for diabetes classification, despite the importance for patient management. Guidance on the classification of the two types of diabetes from major health organisations is limited, and focuses on etiology[8 9], whereas it is insulin production that is the driver for informing treatment decisions. Insulin deficiency/production can be assessed by measurement of C-peptide in either blood or urine[10], but it is rarely measured in clinical practice and current guidelines for diabetes management do not recommend its routine use[1 3 11]. Classification is based primarily on clinical judgement, with younger slimmer patients tending to be classed as Type 1, and older, more obese patients diagnosed as Type 2[8]. However, with obesity increasing in the population and the resulting increase in Type 2 diabetes in the young, this traditional distinction has become less clear[12 13].

Misclassification of diabetes has been shown to occur in 7-15% of cases[13-15], and these studies are likely to underestimate the problem, as they only use clinical "clues" as their reference standard.

The current practice based on etiological guidelines and clinical opinion is clearly insufficient. Pragmatic guidelines on diabetes classification have been developed by NHS Diabetes and The Royal College of General Practitioners in the UK, but are taken from consensus expert clinical opinion rather than being evidence-based[13].

In order to determine evidence based criteria that could be used to classify the two main forms of diabetes, an appropriate gold standard is necessary. The most important reason for correctly classifying patients is to ensure appropriate treatment and management, and the main factor determining this is the difference in endogenous insulin production between patients with Type 1 and Type 2 diabetes. Therefore, long term insulin deficiency represents an acceptable reference standard for Type 1 diabetes. This is likely to be preferable to using markers of the autoimmune process associated with Type 1 diabetes. While measurement of various islet autoantibodies may aid discrimination, these are imperfect measures[16], and most importantly, the presence of islet autoimmunity does not in itself determine treatment requirement[17].

We aimed to systematically review the literature to identify clinical criteria, predictive of severe insulin deficiency, that could be used to discriminate Type 1 diabetes from Type 2 diabetes and inform evidence based guidelines for the classification of diabetes.

**Methods**

We followed the PRISMA guidelines for the reporting of systematic reviews. The original protocol has been published[18] and is registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/ reference CRD42012001736).

*Data sources and search strategy*

14 databases were searched systematically: MEDLINE, MEDLINE in Process, EMBASE, PsycINFO, Social Policy and Practice, AMED, British Nursing Index, CINAHL, HMIC, Sociological Abstracts, ASSIA, Cochrane, Web of Science, Centre for Reviews and Dissemination). The search strategy took the form of: (terms for diabetes) AND (terms for C-Peptide). Searches were limited to human only populations and from 1979 since that was when the original classification scheme was proposed by the National Diabetes Data Group[19]. Searches were not limited by language or study design.

Searches were also carried out on the Conference Proceedings Citation Index as well as the proceedings of the American Diabetes Association, the European Association for the Study of Diabetes, and Diabetes UK. BL Ethos was also searched for theses. Web-searching was conducted, including web-site specific searches of WHO and NICE. Forwards and backwards citation chasing was conducted on all studies included at full-text. The full search strategies are recorded in the online supplemental material (Supplemental Search Annex). Searches were initially performed in October 2012 and were updated on 03/04/14 to capture any additional studies that may have been carried out since the beginning of the review.

*Study selection:*

A two-stage screening process was undertaken. In Stage 1, after removing duplicates, two reviewers (BS and JP) independently screened the titles and abstracts of all references against the inclusion and exclusion criteria. In Stage 2, full texts were retrieved on all studies included at the first screening stage and were independently screened (by BS and JP). Authors of included conference abstracts were searched to determine whether a full article had subsequently been published. Any discrepancies between the two reviewers were discussed and resolved by consensus, or in discussion with a third reviewer (RP).

*Inclusion and exclusion criteria*

Included studies comprised diagnostic accuracy studies of clinical predictors of insulin deficiency, with the reference standard of insulin deficiency being defined by cutoffs of C-peptide results. All measurements of C-peptide and all cutoffs for insulin deficiency were included. Clinical predictors were defined as any routinely measured clinical feature and studies were eligible if there was a cutoff for that clinical predictor assessed against the measure of insulin deficiency. There were no restrictions on race, age, or country of origin. Studies examining islet autoantibodies only were excluded as they are not routinely measured. A separate systematic review examining the diagnostic accuracy of islet autoantibodies is presently underway (Prospero reference CRD42012001736). Studies where patients had known causes of diabetes, e.g. monogenic, secondary or syndromic diabetes, were excluded.

*Data extraction*

For all studies meeting the inclusion and exclusion criteria, data were extracted independently by both reviewers (BS and JP). Data extraction forms were developed and piloted prior to the review. Key details of population (age, sex, country, race, year), diabetes (definition of diabetes, treatment, subgroups), reference standard (type of sample, stimulation, assay, cutoff used), and clinical predictors (which predictors were included, how they were measured, the cutoffs used) were recorded. All C-peptide cutoffs were converted to the fasting serum equivalent to allow direct comparison[10]. Two-by-two tables were extracted where possible to determine the proportion of patients who were C-peptide negative/positive (i.e. below/above the cutoff) and the sensitivity, specificity, positive and negative predictive values of the clinical characteristics at reported cut-offs.

*Quality assessment*

Both reviewers (BS and JP) assessed quality independently and discrepancies were resolved by consensus. Quality assessment forms, based on the criteria set out in QUADAS-2[20], were developed and piloted prior to review. These criteria included assessment of internal and external validity of patient selection, the clinical predictors, and patient flow and timing. Variability in the measurements for the reference standard was assessed separately. Further details are available in the online supplemental material.

*Data synthesis*

Due to the considerable heterogeneity between the studies identified, meta-analysis, as proposed in our original protocol, was not appropriate. Data synthesis is, therefore, largely descriptive with summary data presented. Criteria with a mean of sensitivity and specificity >70% (equivalent to an ROC AUC of 0.7) were considered clinically useful. Ranking of the discriminatory ability of criteria *within* studies was used to compare their relative performance.

*Reporting bias*

No formal assessment of publication bias was undertaken due to heterogeneity between studies and the small number of included studies. We did perform a comprehensive and exhaustive search including grey literature, however it cannot be ruled out that our systematic review is affected by reporting biases.

**Results:**

*Initial screening*

Figure 1 shows the flow diagram of citations found. 10,917 records were identified from database searches and a further 148 sources were identified from grey literature searches. After title and

abstract screening, 194 articles were deemed potentially relevant. Following full-text screening, 9 studies were identified as eligible based on our inclusion criteria[21-29] (for further details see online supplemental material).

Backward and forward citation searching was carried out on the 9 included references, and conference abstracts were followed up, identifying a further 43 studies for full text review, one of which[30] met our inclusion criteria. In April 2014, an update search was performed yielding a further 2101 references for screening. 36 of these were identified by the 2 reviewers as requiring full text review, and 1 of these fitted inclusion criteria[31]. Thus, 11 articles contribute to this systematic review.

*Data Extraction and Quality Assessment*

There was considerable heterogeneity across the included studies (see Supplemental Table 1). The 11 included studies spanned a wide range of years (1981-2013). Studies varied in terms of race, age group, and subgroups of diabetes studied. One study included only patients with end stage renal disease[22], whereas it was a specific exclusion criterion for another study[28]. Three studies focused on insulin treated patients only[24 29 30], whereas the other studies either included all patients regardless of treatment or did not report on treatment. Sample size ranged from <100[22 29 31] to >3000[25]. The proportion of patients classified as insulin deficient (based on the reported C-peptide cutoff in each paper) also varied (median (range) 40% (7% to 69%)), reflecting differing inclusion criteria across studies altering the proportions with different forms of diabetes across the studies.

Quality assessment of the included studies is summarized in Supplemental Table 2. In general, there was a low risk of bias in terms of patient selection and patient flow/timing. Two studies were at high risk of bias[22 29] in terms of the clinical criteria used as these were internally derived, so diagnostic

performance is likely overestimated in these cases[32]. In terms of external validity, studies were all applicable to our broad research question but most restricted inclusion criteria to a subset of the diabetic population.

The reference standards varied in terms of sample provided, timing of sample in relation to meal stimulation, and cutoffs for C-peptide (Supplemental Table 3). Five studies report deriving their cutoffs from previous papers[21 22 25 29 30]. Two studies derived the cutoff used from their own data[27 28], potentially introducing bias, although the cut-offs were comparable to those derived from the literature. Despite the variation in measurements, all were appropriate to classify insulin deficiency and cutoffs were largely comparable with most approximating 0.2nmol/l[21 22 24-26 28 30], and 4 studies using a slightly more conservative cutoff (0.03-0.08nmol/l) [23 27 29 31]. Only one study measured C-peptide and clinical features at diabetes diagnosis[31]. All other studies were cross-sectional with varying duration of diabetes.

*Data synthesis*

Due to the heterogeneity across studies, particularly in terms of inclusion criteria, formal quantitative meta-analysis was not appropriate. Therefore, data synthesis is largely descriptive.

*Age at diagnosis, BMI, insulin treatment/time to insulin are consistent predictors of insulin deficiency across studies.*

Age at diagnosis (9 studies), measures of obesity (including BMI, or percentage desirable weight in earlier studies) (8 studies) and either time to insulin treatment (5 studies) and/or use of insulin treatment (3 studies) were identified as consistent clinical criteria predictive of insulin deficiency (Table 1). In all studies reporting these criteria, younger age at diagnosis, slimmer BMI and shorter time to insulin was used to define insulin deficiency.

Absence of each of acanthosis nigricans and hypertension were predictive of insulin deficiency (overall correct classification rates of 61% and 72%, respectively), but these were only assessed in one study[31]. Other measures were available in four studies[22 26 27 31] (including history of diabetic ketoacidosis[22 26] or ketonuria[22], history of hypoglycemia[27], speed of onset of diabetes[26], long term complications[22], polyuria[22], weight loss[22], post-Sustacal glucose[27], serum creatinine[27], diabetes in a first degree relative[31], and history of poor control[27]), but they were either not discriminatory, or they contributed very little individual discriminatory power to an overall algorithm.

*Age at diagnosis cutoffs better predicted insulin deficiency than cutoffs of BMI or time to insulin*

When comparing discriminative ability of the most commonly reported criteria *within* studies, age at diagnosis, at the cutoff described in the individual study, correctly classified more patients than the other clinical features (most discriminatory criteria in 7/9 studies). Time to insulin/insulin treatment was the next best predictor, and BMI (or equivalent) was the weakest of the significant predictors (Table 1).

*Cutoffs for age at diagnosis, BMI and time to insulin were fairly consistent across studies*

Cutoffs with the best combination of sensitivity and specificity (mean of sensitivity and specificity >70%) were similar across studies. For predicting insulin deficiency, the best cutoffs for age at diagnosis were <30 yrs (2 studies) or </<=40yrs (4 studies). For time to insulin, <1 year (1 study) or </<=2 years (2 studies) were the best cutoffs, although longer cutoffs were not assessed in any of the studies identified. For BMI, cutoffs <27kg/$m^2$ (1 study) and <28kg/$m^2$ (3 studies) were most useful (see Table 2). Extracted 2 x 2 tables are presented Supplemental Tables 4.

*BMI cutoffs provide little improvement in classification in addition to age at diagnosis and insulin use/time to insulin criteria*

Combinations of cutoffs did not consistently improve the overall rate of classification. The addition of BMI did not improve classification over age at diagnosis and/or use of/time to insulin treatment in all 5 studies where these combinations were reported (<1% improvement in classification; see Table 3). The addition of insulin treatment or time to insulin criteria improved classification over using age at diagnosis alone in 3/5 studies where both were reported (see Table 3). Extracted 2 x 2 tables and summary statistics are presented in Supplemental Tables 4 and 5.

## Discussion

### Principal findings

*Few studies have robustly assessed utility of clinical features in diagnosing diabetes subtype*

There were only 11 appropriate studies that examined which clinical characteristics could discriminate between Type 1 and Type 2 diabetes, using the reference standard of insulin deficiency. This is a remarkably low number of studies considering the vast majority of the >200M patients with diabetes will be classified into Type 1 or Type 2 on the basis of clinical features alone and an incorrect classification will result in inappropriate treatment.

*Age at diagnosis was the most discriminatory clinical feature*

Age at diagnosis, time to insulin and BMI consistently emerged as the main discriminatory clinical criteria despite the considerable heterogeneity of the included studies. Age at diagnosis was the best discriminatory criteria with diagnosis either below 30 or below 40 years being predictive of T1D. In

terms of providing useful criteria for clinical practice, based on the current available evidence, this would suggest clinicians should place more emphasis on age than obesity when diagnosing diabetes subtype, but exercise caution when classifying patients diagnosed between the ages of 30 and 40 where further investigation is likely to be necessary.

*Time to insulin treatment is a useful discriminator, but biased by physician opinion*

Commencing insulin treatment before 2 years did slightly improve discrimination over age of diagnosis (Table 3). However, treatment assignment can clearly not be used to define initial treatment, which is one of the major reasons for determining diabetes subtype. Treatment decisions are physician-dependent, as well as disease-dependent, so will vary between clinicians.

*BMI discriminatory but adds little over age at diagnosis*

BMI provided <1% improvement in classification over age at diagnosis or age at diagnosis and time to insulin. Clinicians often use obesity as a marker to indicate Type 2 diabetes, but our findings suggest using this is unlikely to be helpful over and above using age at diagnosis.

*Other may not be sufficiently discriminatory*

Other measures were less often studied. Acanthosis nigricans and hypertension did discriminate C-peptide positive from C-peptide negative patients, but these were only assessed in one study. Other features were either not discriminatory or only contributed weakly to an algorithm, and therefore unlikely to be useful in practice. These measures included features of diagnosis such as diabetic ketoacidosis, ketonuria, and rapid onset of symptoms including weight loss. In fact, in the two studies examining only patients presenting with DKA, 40% and 46% were C-peptide positive[21 31], suggesting DKA is not useful in its own right for classifying a patient as having Type 1 diabetes.

**Strengths and weaknesses**

*Strengths:*

We have carried out a comprehensive and robust systematic review in accordance with PRISMA guidelines and our initial published protocol[18]. We screened a large number of literature sources, and all reviewing and data extraction was carried out in duplicate independently by two authors (BS and JP).

*Limitations:*

Heterogeneity across studies could have influenced the diagnostic performance of cutoffs identified and so precluded formal meta-analysis. There were 4 key areas in particular, where heterogeneity was apparent: 1) The proportion of insulin deficient patients varied considerably across the studies (range 7-69%), reflecting major differences in inclusion criteria for each study, and varying proportions of Type 1 and Type 2 diabetes in the study populations. 2) Studies spanned over 30 years (1981-2013) and there have been considerable changes in the phenotype of Type 1 and Type 2 diabetes in this time. With the rising prevalence of obesity in the population, Type 1 patients are now more likely to be obese than in the past, and Type 2 diabetes has become more common in young adults. 3) Renal disease is known to impact on C-peptide clearance, so differences were likely in the studies excluding patients with renal disease[25 28], compared with those exclusively examining those with ESRD[22]. 4) Ethnicity differed across studies, from populations that were predominantly Caucasian[23 27], to those predominantly Hispanic and/or Black African[31]/African American patients[21 25]. Despite the considerable differences in studies, however, there were consistencies in both the criteria identified and the most discriminatory cutoffs across the different populations.

The small number of studies and the heterogeneity between them means there is still uncertainty around the usefulness of the criteria and cutoffs proposed, and highlights a clear need for further

work in this area. This review provides a strong starting point from which to develop future prediction criteria.

Differences in the reference standards (e.g. in the samples, stimuli, assay used, and cutoffs used) highlighted problems with our reference standard for Type 1 diabetes. However, although cutoffs were derived in a variety of ways, they were largely comparable and appropriate for detecting insulin deficiency in the populations of interest. Where more than one cutoff was used[24 26 27 30], this made little difference (<12%) to the proportion of patients classified and the cutoffs identified. These differences represent potential issues with using our "gold standard" for insulin deficiency when aiming to classify Type 1 diabetes. We would therefore suggest caution in future studies when classifying patients close to the proposed C-peptide cutoff.

*Other forms of diabetes*

We have only considered the two main forms of diabetes for which there are clear national and international treatment guidelines. Rarer subtypes are not considered here. Other forms of diabetes, such as LADA, are not included in international guidelines, and appropriate treatment would be guided by insulin deficiency, our gold standard. Further work would be needed to derive criteria for a "grey area" where diagnosis of subtype is less certain and further investigations would be required to aid classification.

**Implications and Future work:**

Evidence-based guidelines on the classification of T1D and T2D need to include clinical criteria on how the diagnosis should be made. This is a major omission in current national and international guidelines for diabetes. The evidence as identified in this review suggests age at diagnosis and time to insulin (when available) are essential components as they contribute most to the predictive ability. BMI, and other clinical criteria, do not appear to add to add further discrimination. The

criteria identified are similar to the RCGP/NHS Diabetes Guidelines for Classification[13] which are based on consensus expert opinion. These guidelines would therefore, represent a suitable classification scheme until a stronger evidence base is available.

New studies are urgently needed to further develop and validate criteria suitable for classifying diabetes. We identified no studies in the Asian or pediatric populations, and only one study assessing features close to diagnosis[31]. Determining classification rules for both the incident and prevalent population would be important. Labelling a patient's diabetes at the outset is crucial as the classification given is rarely reconsidered. The evidence in this review should be used to redevelop a clinical prediction tool for Type 1 and Type 2 diabetes. C-peptide is likely to be less discriminatory at diagnosis, as patients with Type 1 diabetes can still produce their own insulin in the "honeymoon" period, so it would be important to examine predictors of insulin deficiency after this time. Future studies should be large-scale, prospective, and give results for all racial and age groups using follow-up C-peptide measurements at least 3 years after diagnosis as an outcome. These studies would help answer if clinical criteria used in combination are sufficient to accurately classify diabetes, or whether investigations, such as islet autoantibodies, are needed in addition. Consideration of other forms of diabetes, such as monogenic diabetes, is also important.

We did not include antibodies in our search criteria as we limited our review to routinely available clinical criteria. Antibodies may represent a useful test at diagnosis, where C-peptide is of limited value due to the "honeymoon period", where patients with Type 1 diabetes are still able to produce significant amounts of their own insulin for a short period of time. A systematic review examining the use of antibodies at predicting long term insulin deficiency is presently in progress (Prospero reference CRD42012001736)

In conclusion, we have performed the first systematic review of the literature that examines using clinical criteria for the classification of diabetes. Although, only 11 studies were identified, age at diagnosis, and time to insulin were consistent as discriminatory criteria across studies. BMI did not aid classification over these factors. The discriminatory criteria identified were similar to those proposed by the RCGP/NHS Diabetes Classification guidelines, so these would represent a suitable classification scheme at present. New studies are urgently needed to assess and validate the most appropriate clinical criteria. This review provides a summary of the current knowledge base for reference in any future studies developing classification rules.

**Declarations**:



Declaration of competing interests: All authors have completed the ICMJE uniform disclosure form at and declare: all authors had financial support from the National Institute for Health Research for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributorship: BS designed the review, carried out screening, reviewing, data extraction, quality assessment, and synthesis, and led writing of the manuscript. She is guarantor. JL helped design the

review, carried out screening, reviewing, data extraction, quality assessment, and synthesis (independently, in parallel with BS), and helped draft and revise the manuscript. CC designed the search strategy and performed the initial literature search and revised the draft manuscript. JL performed additional searching, retrieved full text articles for review and revised the draft manuscript. BK and AJ helped design the review, and revised the draft manuscript. RP acted as third reviewer in cases of disagreement for the systematic review and revised the draft manuscript. CH helped design the review, advised on synthesis, and revised the draft manuscript. AH helped design the review, advised on synthesis, and revised the draft manuscript.

Ethics approval was not required for this study as it was only a systematic review of the literature.

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Transparency: The lead author, BS, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had

full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing: No additional data available

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**Figure 1**

Flow diagram showing inclusions and exclusions from title and abstract screening, and full text review. *Follow Up includes full texts identified from follow up of conference abstracts (n=29) and references identified from backwards and forwards citation chasing (n=14).

**Table 1. Criteria reported in the 11 included studies used to discriminate between C-peptide positive and negative patients.**

| First author (year) | Age Diag | Insulin treated or Time to insulin | BMI (or similar) | DKA | Onset (gradual or acute) |
|---|---|---|---|---|---|
| Prior 1991 | 1 | 2 | 3 | | |
| Welborn 1983 | 2 | 1 | 3 | | |
| Laakso 1987 | 3 | 1 | 2 | | |
| Benhamou 1992 | 1 | 2 | 3 | **x** | **x** |
| Shields 2010 | 1 | 2 | 3 | | |
| Service 1997 | # | # | # | # | # |
| Boyle 1999 | 1 | 2 | 3 | | |
| Welborn 1981 | 1 | 2 | | | |
| Nielsen 1986 | 1 | | | | |
| Ekpebegh 2013 | 1 | | 2 | Inc | |
| Balasubramanyam 2006 | | | 1 | Inc | |

Numbers indicate their ranking in terms of discriminatory ability within studies, with 1 representing the most discriminatory. # indicates used as part of an algorithm, but discriminatory value of individual criteria not reported. x indicates features not discriminatory. 'Inc' indicates inclusion criteria for the study, so feature could not be used to discriminate. Only features reported in more than one paper shown (see text for details of others).

**Table 2. Criteria for predicting Type 1 diabetes – single criteria**

| Cutoff | Author (year) | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| **i) Age at diagnosis (a/d)** | | | | | | | | | |
| <20 | Boyle 1999 | 3613 | 7 | 20 | 97 | 59 | 92 | 36 | 94 |
| **<=30** | **Prior 1991** | **575** | **61** | **84** | **82** | **83** | **83** | **88** | **77** |
| **<30** | **Nielsen 1986** | **215** | **69** | **64** | **88** | **76** | **72** | **92** | **53** |
| <30 | Ekpebegh | 71 | 49 | 57 | 72 | 65 | 65 | 67 | 63 |
| **<39** | **Shields 2010** | **72** | **56** | **68** | **97** | **83** | **81** | **96** | **70** |
| **<=40** | **Prior 1991** | **575** | **61** | **97** | **59** | **78** | **82** | **79** | **92** |
| **<=40** | **Welborn 1983** | **121** | **21** | **84** | **85** | **85** | **85** | **60** | **95** |
| **<=40** | **Welborn 1981** | **201** | **24** | **76** | **81** | **79** | **79** | **55** | **92** |
| <=40 | Laakso* 1987 | 171 | 67 | 61 | 79 | 70 | 67 | 85 | 44 |
| <45 | Boyle 1999 | 3613 | 7 | 65 | 57 | 61 | 57 | 10 | 96 |
| **ii) Insulin treatment/Time to insulin (tti) (a=all treatments, i=insulin treated only)** | | | | | | | | | |
| Cutoff | Author (year) | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
| on insulin (a) | Prior 1991 | 575 | 61 | 99 | 25 | 62 | 70 | 68 | 97 |
| **on insulin (a)** | **Welborn 1981** | **201** | **24** | **100** | **70** | **85** | **77** | **49** | **100** |
| **on insulin (a)** | **Boyle 1999** | **3613** | **7** | **91** | **61** | **76** | **63** | **15** | **99** |
| tti<=1.5m (i) | Shields 2010 | 72 | 56 | 80 | 56 | 68 | 69 | 70 | 69 |
| **tti<1y (a)** | **Prior 1991** | **575** | **61** | **92** | **75** | **84** | **85** | **85** | **85** |
| **tti<2y (a)** | **Welborn 1983** | **121** | **21** | **100** | **82** | **91** | **86** | **60** | **100** |
| **tti<=2y (i)** | **Laakso* 1987** | **90** | **67** | **70** | **86** | **78** | **75** | **91** | **58** |

**Table 2. Criteria for predicting Type 1 diabetes – single criteria (continued)**

| **iii) BMI** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cutoff | | N | % C-pep neg | Sens (%) | Spec (%) | Mean sens & spec | % correct | PPV | NPV |
| <20 | Boyle 1999 | 3613 | 7 | 10 | 98 | 54 | 92 | 33 | 94 |
| <25[†] | Prior 1991 | 575 | 61 | 34 | 92 | 63 | 57 | 87 | 47 |
| <25 | Boyle 1999 | 3613 | 7 | 41 | 86 | 64 | 83 | 18 | 95 |
| **<27[†]** | **Prior 1991** | **575** | **61** | **87** | **63** | **75** | **78** | **79** | **76** |
| **<=27[†]** | **Welborn 1983** | **121** | **21** | **80** | **67** | **74** | **69** | **38** | **93** |
| **<=27** | **Laakso* 1987** | **90** | **67** | **76** | **66** | **71** | **73** | **82** | **57** |
| **<28** | **Balasumbryaman 2006** | **294** | **60** | **67** | **86** | **77** | **78** | **79** | **77** |
| <29 | Boyle 1999 | 3613 | 7 | 71 | 57 | 64 | 58 | 11 | 96 |
| <29 | Shields 2010 | 72 | 56 | 78 | 56 | 67 | 68 | 69 | 67 |
| <30 | Ekpebegh | 71 | 49 | 77 | 47 | 62 | 62 | 59 | 68 |

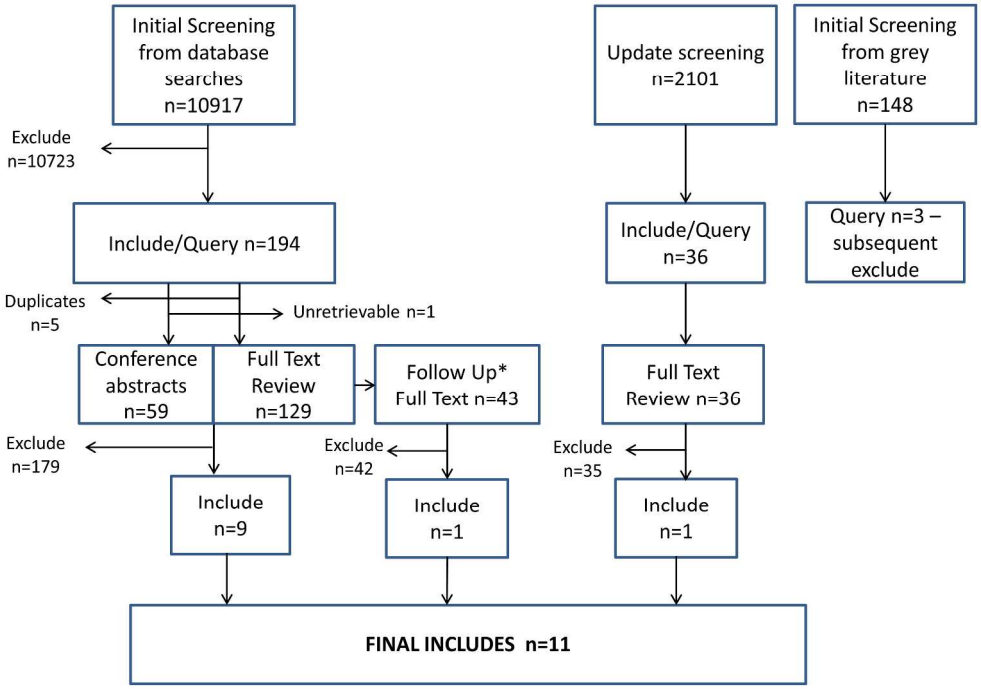
Sensitivity (sens), specificity (spec), proportion correctly classified (%correct), mean of sensitivity and specificity (mean sens & spec), positive predictive value (PPV), and negative predictive value (NPV) for i) age at diagnosis, ii) BMI, and iii) insulin treatment and/or time to insulin. Proportion of C-peptide negative patients (% C-pep neg) shown to aid interpretation of %correct, PPV and NPV. Criteria with a mean sensitivity and specificity >70% are highlighted in bold.

**male and female values combined, using postglucagon-stimulated results [†]converted from percentage desirable weight*

**Table 3** . Comparison of combinations of criteria over individual criteria. Data presented as overall percentage correctly classified according to C-peptide category (below or above cutoff for insulin deficiency) using cutoffs of individual criteria and combinations of criteria, for the 6 studies where comparison within studies was possible. Results in bold are those where the addition of another clinical feature provides better classification within studies, **p<0.01, ***p<0.001, by McNemar's test.

| | | Individual Criteria % correctly classified | | | Combined – 2 criteria % correctly classified | | | Combined – 3 criteria % correctly classified | |
|---|---|---|---|---|---|---|---|---|---|
| Author Year | N | Age at diagnosis | BMI (or equivalent) | Insulin treatment/ Time to insulin (TTI) | Age at diagnosis and BMI | Age at diagnosis and Insulin/TTI | BMI and Insulin/TTI | Age at diagnosis, BMI and Insulin/TTI | Regression equation or algorithm using all 3 criteria |
| Boyle | 3613 (1807[†]) | 92 | 58 | 63 | | 90 | | 93 | 93 |
| Laakso | 171 | 67 | 73 | 75 | 61 | 61 | 67 | 56 | |
| Prior | 575 | 82 | 78 | 85 | | **89*** ** | | 80 | 89 |
| Shields | 72 | 81 | 68 | 69 | | | | 82 | |
| Welborn 1981 | 203 | 79 | | 77 | | **88** ** | | | |
| Welborn 1983 | 121 | 85 | 69 | 86 | | **93** ** | | | 93 |

[†]regression equations/algorithms tested on a separate dataset, so a 2 sample chi-squared test is used to determine statistical significance

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# Online Supplemental Material

## Title: Can clinical features be used to differentiate Type 1 from Type 2 diabetes? A systematic review of the literature.

### Supplemental Methods

Quality Assessment

Quality assessment was based on QUADAS-2, the recommended approach for diagnostic accuracy studies, which considers risk of bias (internal validity) and applicability (external validity) in 4 domains: Patient Selection, Index Tests, Reference Standard and Patient Flow and Timing. Due to potential variations in the measurement of the Reference Standard, this was considered in more detail separately.

*Risk of bias:*
Risk of bias in terms of the way the study was conducted, was assessed by examining patient recruitment, the measurements of the clinical predictors, and recording any exclusions made. Timing of the predictors in relation to the C-peptide measurement was also assessed. Of particular interest was how the clinical criteria were derived.

*Applicability*
When determining external validity, the main point of interest was the inclusion/exclusion criteria, to assess whether the study in question matched our protocol and which subgroups of diabetes patients the study was applicable to. We also aimed to determine whether the clinical predictors (index tests) were applicable to our research question, particularly whether they could be replicated in clinical practice. The timing of these measurements and the reference standard was also of interest, as criteria at diagnosis is likely to differ to criteria measured later on in the course of a patient's diabetes.

*Reference standard*
When assessing the reference standard for insulin deficiency, details such as the sample taken, meal stimulus, and assay used for measurement were examined. C-peptide results were all converted to nmol/l (=0.333*ng/ml) and fasting serum equivalent[1] where necessary, to enable direct comparison. The justification for the cutoff for insulin deficiency was assessed.

### Supplemental Results

*Screening and full text review – further details*
Of 194 potential references, 59 studies were conference abstracts only and 5 were found to be further duplicates. Full texts were retrieved on 129 references. The remaining reference was unretrievable[2]. A further 29 references were identified from follow-up of conference abstracts, 6 of which had been published since the initial screening had been carried out, and full texts were retrieved on these. 11 studies were not in English. These were initially translated using google translate to gauge likely eligibility and in 10 cases it was clear the references were not appropriate. Full translation was required in only one case which appeared to have a table of relevance.

*Full text review - exclusions*
Of the 179 excluded studies at full text review stage, 146 were not diagnostic accuracy studies. 23 were excluded as the reference standard was incorrect (either not C-peptide or other features were incorporated into the reference standard along with C-peptide). 10 were excluded as the index test is not routinely measured (islet antibodies or HLA-alleles).

**Supplemental Table 1** – Summary data extracted from the 10 included papers.

| Author Year | Country | Year of study | Race of population | Sample size | Inclusion (I)/ Exclusion (E) | Treatments | Age group of pop'n | % Male | Prop'n with BMI below cutoff used | Prop'n C-peptide negative |
|---|---|---|---|---|---|---|---|---|---|---|
| Balasubramanyam 2006 | USA (Texas) | 1999-2003 | 44.8% African American; 43.5% Hispanic; 10.8% Caucasian; <1% Asian | 294 | I: Presented with DKA | Unclear – assume all treatments | | 60% | Cutoff of 28kg/$m^2$ = 44$^{th}$ centile | 40% |
| Benhamou 1992 | France | 1989-1990 | Not specified | 88 | I: End stage renal disease | All treatments | Not specified | ? | Unable to extract | 16% |
| Boyle 1999 | USA (Georgia) | 1991-1996 | All African American | 3613 (1807 for testing) | E: Serum creatinine >2mg/dl<br>E: Missing data | All treatments | Split by category – table 1 | 37% | 45% patients BMI≤29 | 7% |
| Ekpebegh 2013 | South Africa | 2010-2012 | Black African | 71 | I: Diagnosis of DKA | All treatments | Mean 34.7+/-15.3 | 54% | 65% BMI<30 | 49% |
| Laakso 1987 | Finland | 1987 | Not specified | 171 | I: Insulin treated only<br>I: aged 45-64 living in region of Kuopio central Hospital | Insulin treated only | Range 45-64 | 47% | 49% of patients BMI≤27 | 67% |
| Nielsen 1986 | Denmark | 1979-1980 | Not specified | 215 | I: Insulin treated only | Insulin treated Only | Not specified | 52% | - | 69% |
| Prior 1991 | USA (Baltimore) | 1980-1985 | 96.5% White | 575 | I: Mild-severe non-proliferative or early proliferative diabetic retinopathy; I: Aged 18-70 | All treatments | Range 18-70 | ? | 68% PDW<120%[a] | 61% |
| Service 1997 | USA (Rochester) | 1986 | Not specified | 346 | No specific exclusion criteria | All treatments | Not specified | ? | Unable to extract | 30% |
| Shields 2010 | UK | 2010 | Not specified | 72 | I: Insulin treated only<br>E: <5y duration and on insulin <2y of diagnosis | Insulin treated only | Adults | ? | 63% BMI<29 | 56% |
| Welborn 1981 | Australia | 1981 | Not specified | 201 | E: Known renal failure | All treatments | Mean 53 +/- 17 for hosp; 55 +/-16 for country | 53% | 43% of cohort PDW≤120%[a] | 24% |
| Welborn 1983 | Australia | 1983 | All Caucasian | 121 | No exclusions for food, glucose or renal status | Unclear – assume all | Adults | ? | Not specified | 21% |

[a]120% PDW (percentage desirable weight) equates to BMI<27.2 for men, <26.9 for women.

**Supplemental Table 2** - Quality Assessment of internal validity (risk of bias) and external validity (applicability of study) for included studies in terms of a) patient selection, b) the index tests and c) patient flow and timing. ✓ = low risk of bias/valid study, ? = risk of bias/validity unclear, ✗= high risk of bias/problems with validity

| **a) Patient Selection** | | | | |
|---|---|---|---|---|
| **Author Year** | **Internal Validity**<br>**Risk of bias in patient selection?** | | **External Validity**<br>**Does the study match our question?** | |
| Balasubramanyam 2006 | ✓ | Low. Consecutive recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides. | ✓ | Applicable only for those who have presented with DKA. |
| Benhamou 1992 | ✓ | Low. Random recruitment. Excluded secondary diabetes and missing data | ✓ | Applicable for ESRD patients only. Very few details of population |
| Boyle 1999 | ✓ | Low. New patients enrolled (random) – not all at diagnosis. Excluded renal disease and missing data | ✓ | Applicable for African American non renal disease group only |
| Ekpebegh 2013 | ? | Unclear – cross sectional but few details on recruitment. By choosing only those who have presented with DKA, possible bias toward those with lower C-peptides. | ✓ | Applicable only for those who have presented with DKA and Black African racial group. |
| Laakso 1986 | ✓ | Low. Random recruitment – 78% recruitment rate. | ✓ | Applicable for insulin treated patients only. Older patients |
| Nielsen 1986 | ✓ | Low. Consecutive recruitment. | ✓ | Applicable for insulin treated patients only. |
| Prior 1991 | ? | Unclear. 582/3711 with C-peptide measurements available. Possible selection bias as those with C-pep measured different from rest (diagnosed older, less likely to be insulin treated and slimmer) | ✓ | Applicable for patients with retinopathy only. 95% White. |
| Service 1997 | ✓ | Low. Cross-sectional survey. Representative of all diabetes 10-70 in Rochester area | ✓ | Applicable to Rochester population aged 10-70 |
| Shields 2010 | ✓ | Low. Recruited through retinal screening. Excluded non-insulin treated and short duration and long time to insulin. | ✓ | Applicable for insulin treated adults only. >5y duration; insulin treated within 2y of diagnosis |
| Welborn 1981 | ? | Unclear, likely random recruitment. Excluded renal failure | ✓ | Applicable for all except renal failure which was excluded in hospital clinic patients. |
| Welborn 1983 | ? | Unclear. Possibly some of same patients as other Welborn paper | ? | Unclear |

| **b) Index Test (Clinical Predictors)** | | | | |
|---|---|---|---|---|
| **Author** | **Internal Validity**<br>**Is there a risk of bias in the way the index tests were measured/cutoffs derived?** | | **External Validity**<br>**Are the measurements applicable for our question?** | |
| Balasubramanyam 2006 | ✓ | Low. Prespecified – objective measures | ✓ | BMI applicable – assume taken close to DKA episode. |

| | | | | |
|---|---|---|---|---|
| Benhamou 1992 | × | High. Regression equation internally derived. Mix of self report/questionnaire – possible recall bias. Unclear how BMI measured | × | Maximum BMI difficult to replicate as dependent on how many and when repeat measurements are taken. |
| Boyle 1999 | ✓ | Low. Systematic assessment – height and weight measured (ref 21). Clinical rules CRI and CRII prespecified. Others not defined but split validation used. | ✓ | Yes – BMI cutoff results applicable to African American population. |
| Ekpebegh 2013 | ? | Unclear for age at diagnosis. Low for BMI - Systematic assessment and cutoffs defined in advance. | ✓ | Yes. |
| Laakso 1986 | ? | Unclear. Assumed taken off register so unlikely recall bias. Unclear when BMI measured. Lack of detail | ✓ | Yes. |
| Nielsen 1986 | ? | Unclear. Little detail on how cutoffs derived. | ✓ | Yes. |
| Prior 1991 | ✓ | Low. Clinical rules pre-specified | ✓ | Yes |
| Service 1997 | ✓ | Low. Algorithm pre-specified based on NDDG guidelines. | ? | |
| Shields 2010 | × | High – cutoffs internally derived. Age at diagnosis, BMI and time to insulin all self reported – possible recall bias | ? | Unclear. BMI taken at time of study so may not be valid at other time points |
| Welborn 1981 | ? | Unclear how criteria chosen.<br>Height and weight measured, but no details on how age at diagnosis and treatment were recorded – potential recall bias if patient reported. | ✓ | Yes. |
| Welborn 1983 | ? | Unclear. No details of how key criteria obtained. | ✓ | Unclear. Very little detail, but similar study to Welborn 1981; possible overlap. |

| **c) Patient Flow and Timing** | | | | |
|---|---|---|---|---|
| **Author** | **Internal Validity**<br>**Could exclusions have introduced bias?** | | **External Validity**<br>**Are the timings in the study applicable to our question?** | |
| Balasubramanyam 2006 | ? | Unclear. Doesn't state numbers due to missing data | ✓ | Applicable to first 12 months following DKA episode (not necessarily at diagnosis of diabetes). |
| Benhamou 1992 | ✓ | Low. C-peptide measured on random selection of patients | ? | Unclear. Cross sectional. Duration of diabetes not reported. |
| Boyle 1999 | ✓ | Low. Measures taken at time of enrolment. | ? | Median diabetes duration 1y but variability around that. |
| Ekpebegh 2013 | ✓ | Unclear . No exclusions reported. | ✓ | Applicable to cases presenting with DKA, first manifestation of diabetes. |
| Laakso 1986 | ? | Unclear. No exclusions reported. | ? | Cross-sectional. Unclear when measured in relation to C-peptide. |
| Nielsen 1986 | ? | Unclear. Small subset with C-peptide | ? | Cross-sectional. Don't know when baseline visit is in relation to diabetes duration. |
| Prior 1991 | ? | Unclear. 346/381 with C-peptide measured. Not clear why | ? | Cross sectional. Don't know when visit is in terms |

| | | | | |
|---|---|---|---|---|
| | | some missing, but low numbers. | | of duration of disease |
| Service 1997 | ✓ | Low. 11 deaths and 1 refusal – potentially lost those with lower C-peptide but small numbers. | ✓ | Yes. Some data split by duration. |
| Shields 2010 | ✓ | Low. C-peptide measures were not included for 46 patients in analysis as either <3h post-food or abnormal renal function. Better for reference standard; timing of sample unlikely to be a bias of people entering the study. | ? | Unclear. Duration of diabetes not reported so cannot determine when results would be applicable in time course of diabetes. |
| Welborn 1981 | ? | Unclear. Likely similar to above, as same authors and similar study. | ? | Unclear |

**Supplemental Table 3.** Reference standard C-peptide cutoffs for insulin deficiency. Cutoffs ordered from lowest to highest. Data presented for each study: cutoff as originally described, cutoff converted to nmol/l, fasting serum equivalent[a] to allow direct comparison across studies, assessment of the justification of the cutoff for insulin deficiency, and its applicability. For studies that reported two cutoffs, the most discriminatory is presented.

| Author of study | Cutoff for insulin deficiency in original units; sample type; stimulus used | Cutoff converted to nmol/l, fasting serum[a] | How was cutoff chosen? | Cutoff applicable? |
|---|---|---|---|---|
| Prior 1993 | 80 pmol/l; plasma; post-sustacal | 0.03 nmol/l | Unclear. ?chosen to maximise clinical diffs. | Yes, but likely to be internally derived. Very few patients between 0.04 and 0.32 nmol/l so any cutoff in this range would have led to similar results. |
| Welborn 1983 | 0.16 nmol/l; blood (plasma?); random | 0.06 nmol/l | References Welborn 1981 | Yes, although cutoff described based on fasting samples, whereas in this study samples were taken without reference to food ingestion. |
| Ekpebegh 2013 | 0.5 ng/mL; serum; stimulated | 0.07 nmol/l | Not specified. | Unclear - consistent with other studies, but patients recruited close to diagnosis so C-peptide may be affected by “honeymoon" period. |
| Shields 2010 | 0.2 nmol/mmol; urine C-peptide creatinine ratio; post-meal | 0.08 nmol/l | As reported by Besser et al[3]. to discriminate Type 1 diabetes from MODY. | Yes. |
| Service 1997 | 0.17 pmol/ml; blood (plasma?); fasting (and post-glucagon increment <0.07[b]) | 0.17 nmol/l | “Arbitrarily segregated” … “using previously published criteria for the characterization of IDDM and NIDDM”. No reference provided | Unclear from paper but consistent with Welborn 1981. Results at different cutoffs for fasting and increment are also presented. |
| Welborn 1981 | 0.16 nmol/l; serum; fasting | 0.16 nmol/l | <0.16 well outside 2SDs of mean and exclusively identifies those on insulin therapy. | Yes, but internally derived - insulin use possibly used to determine the reference standard. |
| Benhamou 1992 | 0.6 ng/ml; plasma; fasting | 0.2 nmol/l | DCCT[4] – No IDDM patients had fasting C-peptide >0.6ng/ml 5 years after diagnosis | Yes. |
| Nielsen 1986 | 0.20 pmol/ml; plasma; fasting | 0.2 nmol/l | Reference Madsbad et al[5]. from discriminating insulin from non-insulin treated patients | Yes. |
| Laakso 1987 | 0.60 nmol/l; blood; post-glucagon | 0.2 nmol/l | Not specified. | Unclear, but consistent with other studies. |
| Balasumbryaman 2006 | 1 ng/ml; serum; fasting OR 1.5 ng/ml; serum; post-glucagon | 0.3 nmol/l OR 0.2 nmol/l | Referenced Maldonado et al[6]. where cutoff obtained from ROC analysis in a “relevant population” | Yes. |
| Boyle 1999 | 0.9 ng/ml; not specified (likely plasma); fasting | 0.3 nmol/l | Shows histogram and references 6 papers (although 0.9 ng/ml not used as a cutoff in these papers) | Unclear but consistent with other cutoffs reported. |

[a]All converted to nmol/l (=0.333*ng/ml); urine to serum, and stimulated to fasting C-peptide (fasting=stimulated/2.5 formula unpublished but derived from MMTT data[78]; 0.2nmol/mmol UCPCR=0.2nmol/l stimulated serum C-peptide as described in the review by Jones et al[1]). [b]More than one cutoff reported in the paper.

**Supplemental Tables 4**. Two-by-two tables of clinical criteria cutoffs against reference standard C-peptide cutoffs for insulin deficency. Data extracted either directly as reported in the paper, or indirectly using reported estimates of sensitivity/specificity or positive/negative predictive value, and sample size and proportion of C-peptide negative/positive. C-peptide negative and C-peptide positive are determined as values below or above the cutoff for insulin deficiency reported in the paper.

**Single criteria:**

Balasumbryaman 2006

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <28kg/m$^1$** | 142 | 42 | 184 |
| **BMI>=28kg/m$^2$** | 23 | 86 | 109 |
| | 165 | 128 | 293* |

*1 result missing

Boyle 1999

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20y** | 50 | 88 | 138 |
| **Age at diagnosis >=20y** | 195 | 3280 | 3475 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <45y** | 160 | 1455 | 1615 |
| **Age at diagnosis >=45y** | 85 | 1913 | 1998 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <20 kg/m$^2$** | 25 | 51 | 76 |
| **BMI>=20 kg/m$^2$** | 220 | 3317 | 3537 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<25 kg/m$^2$** | 100 | 462 | 562 |
| **BMI>=25 kg/m$^2$** | 145 | 2906 | 3051 |
| | 245 | 3368 | 3613 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <29 kg/m$^2$** | 175 | 1463 | 1638 |
| **BMI>=30 kg/m$^2$** | 70 | 1905 | 1975 |
| | 245 | 3368 | 3613 |

Ekpebegh 2013

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <30y** | 20 | 10 | 30 |
| **Age at diagnosis >=30y** | 15 | 26 | 41 |
| | 35 | 36 | 71 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<30kg/m$^2$** | 27 | 19 | 46 |
| **BMI>=30kg/m$^2$** | 8 | 17 | 25 |
| | 35 | 36 | 71 |

Laakso 198

using postglucagon male and female combined as the most discriminative

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 70 | 12 | 82 |
| **Age at diagnosis >40y** | 45 | 44 | 89 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=2y** | 80 | 8 | 88 |
| **Time to insulin >2y** | 35 | 48 | 83 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI<=27kg/m$^2$** | 87 | 19 | 106 |
| **BMI >27kg/m$^2$** | 28 | 37 | 65 |
| | 115 | 56 | 171 |

Nielsen 1986

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30y** | 95 | 8 | 103 |
| **Age at diagnosis >30y** | 53 | 59 | 112 |
| | 148 | 67 | 215 |

Prior 1991

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30y** | 295 | 40 | 335 |
| **Age at diagnosis >30y** | 56 | 184 | 240 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 340 | 91 | 431 |
| **Age at diagnosis >40y** | 11 | 133 | 144 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **PDW<100%** | 118 | 17 | 135 |
| **PDW>=100%** | 233 | 207 | 440 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **PDW<120%** | 306 | 83 | 389 |
| **PDW>120%** | 45 | 141 | 186 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **On insulin** | 349 | 168 | 517 |
| **Off insulin** | 2 | 56 | 58 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <1y** | 322 | 56 | 378 |
| **Time to insulin >=1y** | 29 | 168 | 197 |
| | 351 | 224 | 575 |

Shields 2010

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <39y** | 27 | 1 | 28 |
| **Age at diagnosis >=39y** | 13 | 31 | 44 |
| | 40 | 32 | 72 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **BMI <29kg/m$^2$** | 31 | 14 | 45 |
| **BMI>=29kg/m$^2$** | 9 | 18 | 27 |
| | 40 | 32 | 72 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=1.5m** | 32 | 14 | 46 |
| **Time to insulin >1.5m** | 8 | 18 | 26 |
| | 40 | 32 | 72 |

Welborn 1983

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| | | | |

| | | | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 21 | 14 | 35 |
| **Age at diagnosis >40y** | 4 | 82 | 86 |
| | 25 | 96 | 121 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **PDW<=120%** | 20 | 32 | 52 |
| **PDW>120%** | 5 | 64 | 69 |
| | 25 | 96 | 121 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **Time to insulin <2y** | 25 | 17 | 42 |
| **Time to insulin >2y + not on insulin** | 0 | 79 | 79 |
| | 25 | 96 | 121 |

Welborn 1981

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **Age at diagnosis <=40y** | 35 | 29 | 64 |
| **Age at diagnosis >40** | 11 | 126 | 139 |
| | 46* | 155 | 203 |

| | **C-peptide negative** | **C-peptide positive** | |
|---|---|---|---|
| **On insulin** | 48 | 47 | 95 |
| **Off insulin** | 0 | 108 | 108 |
| | 48 | 155 | 203 |

**Combined criteria**

Boyle 1999

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 and insulin treated** | 33 | 104 | 137 |
| **Other** | 74 | 1596 | 1670 |
| | 107 | 1700 | 1807 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 insulin treated and BMI <26** | 16 | 27 | 43 |
| **Other** | 91 | 1673 | 1764 |
| | 107 | 1700 | 1807 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <28.9 insulin treated and BMI <31.7** | 26 | 49 | 75 |
| **Other** | 81 | 1651 | 1732 |
| | 107 | 1700 | 1807 |

Laakso 1987

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 and time to insulin <=2y** | 51 | 2 | 53 |
| **Opposite** | 64 | 54 | 118 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 and BMI <=27** | 53 | 5 | 58 |
| **Opposite** | 62 | 51 | 113 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Time to insulin <=2y and and BMI <=27** | 63 | 4 | 67 |
| **Opposite** | 52 | 52 | 104 |
| | 115 | 56 | 171 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=40 , time to insulin <=2y and and BMI <=27** | 40 | 1 | 41 |
| **Opposite** | 75 | 55 | 130 |
| | 115 | 56 | 171 |

Prior 1991

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30, time to insulin <=1y and PDW<120%** | 248 | 11 | 259 |
| **Opposite** | 103 | 213 | 316 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <=30, time to insulin <=1y OR ad<40, tti<1y PDW<120%** | 309 | 22 | 331 |
| **Opposite** | 42 | 202 | 244 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20, time to insulin immediately** | 238 | 16 | 254 |
| **Other** | 113 | 208 | 321 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age at diagnosis <20, time to insulin immediately OR Age at diagnosis >=20, time to insulin immediately PDW<=120%** | 328 | 61 | 389 |
| **Other** | 23 | 163 | 186 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <30 tti <1y** | 277 | 15 | 292 |
| **Other** | 74 | 209 | 283 |
| | 351 | 224 | 575 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <40 tti <1y** | 313 | 28 | 341 |
| **Other** | 38 | 196 | 234 |
| | 351 | 224 | 575 |

Welborn 1983

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <40 and tti<=2y** | 21 | 4 | 25 |
| **Other** | 4 | 92 | 96 |
| | 25 | 96 | 121 |

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag <=40y tti<2y OR age diag>40y tti<2y and PDW<120%** | 23 | 6 | 29 |
| **Other** | 2 | 90 | 92 |

| | | | |
|---|---|---|---|
| | 25 | 96 | 121 |

Welborn 1981

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Age diag<=4-y and on insulin** | 35 | 12 | 47 |
| **Other** | 13 | 143 | 156 |
| | 48 | 155 | 203 |

**Equations or algorithms**

Service 1997

Algorithm:
Type 1=insulin treated+ketosis+slim OR insulin treated, no ketosis, diagnosed <=21y and acute onset

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **Type 1 acc to algorithm** | 74 | 25 | 99 |
| **Other** | 10 | 237 | 247 |
| | 84 | 262 | 346 |

Benhamou 1992

Regression equation = T=(0.01166*time to insulin)+(0.01324*age diagnosis)+(0.01188*BMI max)-0.22834.

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **T<=0.5** | 14 | 3 | 17 |
| **T>0.5** | 0 | 71 | 71 |
| | 14 | 74 | 88 |

Boyle 1999

Regression equation =
Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI)

| | C-peptide negative | C-peptide positive | |
|---|---|---|---|
| **T1 prob>0.2** | 55 | 153 | 208 |
| **T1 prob<=0.2** | 52 | 1547 | 1599 |
| | 107 | 1700 | 1807 |

**Supplemental Table 5 Criteria for predicting insulin deficiency – combined criteria**

| Age at diagnosis (a/d) and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| a/d<=40 BMI<=27 | Laakso 1987 | 46 | 91 | 61 | 91 | 45 | 67 |

| Time to insulin (tti) and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| tti<=2 BMI<=27 | Laakso 1987 | 55 | 93 | 67 | 94 | 50 | 67 |

| Age at diagnosis and time to insulin | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **a/d<=20 tti immed** | **Prior 1991** | **68** | **93** | **78** | **94** | **65** | **61** |
| **a/d<30 tti<1y** | **Prior 1991** | **79** | **93** | **85** | **95** | **74** | **61** |
| ad<30 on insulin | Boyle 1999 | 31 | 94 | 90 | 76 | 96 | 7 |
| **ad <=40 on insulin** | **Welborn 1981** | **73** | **92** | **88** | **74** | **92** | **24** |
| **a/d<40 tti<1y** | **Prior 1991** | **89** | **88** | **89** | **92** | **84** | **61** |
| **ad<=40 tti<=2** | **Welborn 1983** | **84** | **96** | **93** | **84** | **96** | **21** |
| a/d<=40 tti<=2 | Laakso 1987 | 44 | 96 | 61 | 96 | 46 | 67 |

| Age at diagnosis, tti and BMI | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **a/d<20 tti immed OR a/d>=20 ins immed PDW<=120** | **Prior 1991** | **93** | **73** | **85** | **84** | **88** | **61** |
| ad<28.9 on ins bmi<31.7 | Boyle 1999 | 24 | 97 | 93 | 35 | 95 | 7 |
| **a/d<30 tti<1y PDW<120%** | **Prior 1991** | **71** | **95** | **80** | **96** | **67** | **61** |
| **a/d<30 tti<1 OR a/d<40 tti<1 PDW<120%** | **Prior 1991** | **88** | **90** | **91** | **93** | **83** | **61** |
| ad<30 on ins BMI<26 | Boyle 1999 | 15 | 98 | 93 | 37 | 95 | 7 |
| a/d<=40 tti<=2 BMI<=27 | Laakso 1987 | 35 | 98 | 56 | 98 | 42 | 67 |
| **ad<=40 tti<2 OR ad>40 tti<2 PDW<120%** | **Welborn 1983** | **92** | **94** | **93** | **79** | **98** | **21** |

| Equations or algorithms | Author | Sensitivity | Specificity | % correctly classified | PPV | NPV | % C-pep negative |
|---|---|---|---|---|---|---|---|
| **Algorithm: Ins treated & ketosis & ≤120%PDW OR** | **Service 1997** | **75** | **96** | **90** | **88** | **90** | **24** |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Ins treated & no ketosis & age diag<21y & acute onset** | | | | | | | |
| **Regression equation (T1 if >0.5): (0.0116*tti)+(0.01324*age diag)+(0.01188*BMI)** | **Benhamou 1992** | **100** | **96** | **97** | **82** | **100** | **16** |
| Regression equation (T1=prob>0.2) Log OR=1.09+(2.19if ins treated)-(0.031*age diag)-(0.127*BMI) | Boyle 1999 | 51 | 91 | 89 | 26 | 97 | 7 |
| Classification tree: Insulin treated, diagnosed<28.9 and BMI<31.7 | Boyle 1999 | 24 | 97 | 93 | 35 | 95 | 7 |
| Classification tree including age diag, tti and BMI: *Details not reported* | Shields 2010 | | | 82 | | | |

**Supplemental Search Annex**

| Database | Hits |
|---|---|
| 1. MEDLINE | 5804 |
| 2. MEDLINE in Process | 205 |
| 3. EMBASE | 8566 |
| 4. PsycINFO | 23 |
| 5. Social Policy and Practice | 0 |
| 6. AMED | 11 |
| 7. British Nursing Index (BNI) | 11 |
| 8. CINAHL | 24 |
| 9. HMIC | 5 |
| 10. Sociological Abstracts | 3 |
| 11. ASSIA | 2 |
| 12. Cochrane (all) | 1611 (1613 2 from methods) |
| 13. Web of Science (Conference Proceedings Citation Index) | 4792 |
| 14. Centre for Reviews and Dissemination | 3 |
| Total | 21060 |
| Duplicates Removed | -10143 |
| Unique Records | 10917 |

1.
**Database:** MEDLINE
**Host:** OVID
**Data Parameters:** 1946 to October Week 2 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 5804
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 57591 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 29301 |
| 3 | (T1DM or dm1).ti,ab. | 2338 |
| 4 | diabet$.ti,ab. | 348751 |
| 5 | 1 or 2 or 3 or 4 | 355909 |
| 6 | C-Peptide/ | 6951 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 8707 |
| 8 | "Connecting Peptide$".ti,ab. | 292 |
| 9 | 6 or 7 or 8 | 11014 |
| 10 | 5 and 9 | 6230 |
| 11 | exp animals/ not humans.sh. | 3795620 |
| 12 | 10 not 11 | 5897 |

| | | |
|---|---|---|
| 13 | limit 12 to yr="1979 -Current" | 5804 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** Medline Endnote RIS n=5804.txt

2.
**Database:** Medline in Process
**Host:** OVID
**Data Parameters:** October 22nd , 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits: 205**
**Strategy:**

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 1502 |
| 3 | (T1DM or dm1).ti,ab. | 222 |
| 4 | diabet$.ti,ab. | 17913 |
| 5 | 1 or 2 or 3 or 4 | 17961 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 285 |
| 8 | "Connecting Peptide$".ti,ab. | 8 |
| 9 | 6 or 7 or 8 | 291 |
| 10 | 5 and 9 | 205 |
| 11 | exp animals/ not humans.sh. | 3 |
| 12 | 10 not 11 | 205 |
| 13 | limit 12 to yr="1979 -Current" | 205 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** Medline in Process RIS n=205.txt

**3.**
**Database:** Embase
**Host:** OVID
**Data Parameters:** Embase 1980 to 2012 Week 42, Embase 1974 to 1979
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 8566
**Strategy:**

Search Strategy:

| # | Searches | Results |
|---|---|---|

| | | |
|---|---|---|
| 1 | insulin dependent diabetes mellitus/ | 70536 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 41404 |
| 3 | (T1DM or dm1).ti,ab. | 4248 |
| 4 | diabet$.ti,ab. | 495933 |
| 5 | 1 or 2 or 3 or 4 | 507285 |
| 6 | C peptide/ | 11467 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 11576 |
| 8 | "Connecting Peptide$".ti,ab. | 307 |
| 9 | 6 or 7 or 8 | 14807 |
| 10 | 5 and 9 | 8775 |
| 11 | exp animal/ not human/ | 1352023 |
| 12 | 10 not 11 | 8718 |
| 13 | limit 12 to yr="1979 -Current" | 8566 |

**Limits:** The search is limited to human only populations and by date to 1979-Current.
**Notes:** N/A
**File Name:** Embase Endnote RIS n=8566.txt

**4.**
**Database:** PsycINFO
**Host:** OVID
**Data Parameters:** 1806 to October Week 3 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 23
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 1197 |
| 3 | (T1DM or dm1).ti,ab. | 178 |
| 4 | diabet$.ti,ab. | 16010 |
| 5 | 1 or 2 or 3 or 4 | 16087 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 70 |
| 8 | "Connecting Peptide$".ti,ab. | 1 |
| 9 | 6 or 7 or 8 | 71 |
| 10 | 5 and 9 | 25 |
| 11 | exp animals/ not humans.sh. | 250508 |
| 12 | 10 not 11 | 23 |

| | | |
|---|---|---|
| 13 | limit 12 to yr="1979 -Current" | 23 |

**Limits:** Search limited to human only populations and by date
**Notes:** N/A
**File Name:** PsycINFO Endnote RIS n=23.txt

**5.**
**Database:** Social Policy and Practice (SPP)
**Host:** OVID
**Data Parameters:** 201207
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 0
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 59 |
| 3 | (T1DM or dm1).ti,ab. | 0 |
| 4 | diabet$.ti,ab. | 839 |
| 5 | 1 or 2 or 3 or 4 | 839 |
| 6 | C-Peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 0 |
| 8 | "Connecting Peptide$".ti,ab. | 0 |
| 9 | 6 or 7 or 8 | 0 |
| 10 | 5 and 9 | 0 |
| 11 | exp animals/ not humans.sh. | 0 |
| 12 | 10 not 11 | 0 |
| 13 | limit 12 to yr="1979 -Current" | 0 |

**Limits:** N/A
**Notes:** N/A
**File Name:** No File Recorded

6.
**Database:** AMED
**Host:** Ebsco Host
**Data Parameters:** 1995-Current
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 11
**Strategy:**

TI diabet* OR AB diabet*
TI ( ((c-peptide*) or (c peptide*)) ) OR AB ( ((c-peptide*) or (c peptide*)) )
TI "Connecting Peptide*" OR AB "Connecting Peptide*"
S2 or S3
(S2 or S3) AND (S1 and S4)

**Limits:** None Used

**Notes:** N/A
**File Name:** Amed Endnote RIS n=11.txt

7.
**Database:** British Nursing Index (BNI)
**Host:** ProQuest
**Data Parameters:** 1994-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 11
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A
**File Name:** BNI Endnote RIS n=11

8.
**Database:** Cinahl
**Host:** Ebsco Host
**Data Parameters:** 1981-Current
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 24
**Strategy:**

TI diabet* OR AB diabet*
Search modes - Boolean/Phrase

TI ( (("c peptide*") or (c-peptide*) or (connecting peptide*)) ) OR AB ( (("c peptide*") or (c-peptide*) or (connecting peptide*)) )
Search modes - Boolean/Phrase

S1 and S2
Search modes - Boolean/Phrase

S1 and S2
Limiters - Exclude MEDLINE records
Search modes - Boolean/Phrase

**Limits:** N/A
**Notes:** A server-side de-duplication was run to exclude Medline records.
**File Name:** Cinahl Endnote RIS n=24.txt

9.
**Database:** HMIC
**Host:** OVID
**Data Parameters:** 1979 to September 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 5
**Strategy:**

| # | Searches | Results |
|---|---|---|
| 1 | exp Diabetes Mellitus, Type 1/ | 0 |

| | | |
|---|---|---|
| 2 | ((typ$ 1 or typ$ I or type 1) adj3 diabet$).ti,ab. | 132 |
| 3 | (T1DM or dm1).ti,ab. | 3 |
| 4 | diabet$.ti,ab. | 3553 |
| 5 | 1 or 2 or 3 or 4 | 3553 |
| 6 | C peptide/ | 0 |
| 7 | (c-peptide$ or c peptide$).ti,ab. | 10 |
| 8 | "Connecting Peptide$".ti,ab. | 0 |
| 9 | 6 or 7 or 8 | 10 |
| 10 | 5 and 9 | 5 |
| 11 | exp animal/ not human/ | 0 |
| 12 | 10 not 11 | 5 |
| 13 | limit 12 to yr="1979 -Current" | 5 |

**Limits:** Date limited 1979-Current
**Notes:** N/A
**File Name:** HMIC Endnote RIS n=5.txt

10.
**Database:** Sociological Abstracts
**Host:** ProQuest
**Data Parameters:** 1963-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 3
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A
**File Name:** Soc Abs Endnote RIS n=3

11
**Database:** ASSIA
**Host:** ProQuest
**Data Parameters:** 1987-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 2
**Strategy:**

1. ti((diabet*)) OR ab((diabet*))
2. ti((("c peptide*") or (c-peptide*) or (connecting peptide*))) OR ab((("c peptide*") or (c-peptide*) or (connecting peptide*)))
3. 1 AND 2

**Limits:** None Used
**Notes:** N/A

**File Name:** Assia Endnote RIS N=2

12.
**Database:** Cochrane Library
**Host:** http://www.thecochranelibrary.com/view/0/index.html
**Data Parameters:** Issue 10 of 12, Oct 2012
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 1611 (Reviews: 127; DARE: 20; Central 1449; HTA 3; NHS EEDS 12)
**Strategy:**

#1 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#2 ((typ* 1 or typ* I or type 1) near/3 diabet*)
#3 (T1DM or dm1)
#4 diabet*
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [C-Peptide] explode all trees
#7 ((c-peptide*) or (c peptide*))
#8 "Connecting Peptide*"
#9 #6 or #7 or #8
#10 #5 and #9

**Limits:** N/A
**Notes:** N/A
**File Name:**

13.
**Database:** Web of Science
**Host:** ISI
**Data Parameters:** 1900-Present. SSCI, 1975-Present
**Date Searched:** Tuesday, 23rd October 2012
**Hits:** 4792
**Strategy:**

Topic=(diabet*) AND Topic=((("c peptide*") or ("c-peptide*") or ("connecting peptide*")))
Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=1979-01-01 - 2012-10-23
Lemmatization=Off

**Limits:** Lemmatization=Off. The search was limited by date 1979-Current
**Notes:** SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH were all searched
**File Name:** WOS Endnote RIS n=4792

14.
**Database:** CRD
**Host:** http://www.york.ac.uk/inst/crd/index.htm
**Data Parameters:** 1989-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 3
**Strategy:**

**(diabet*) AND ((("c peptide*") or (c-peptide*) or (connecting peptide*))) FROM 1979 TO 2012**

**Limits:** Date Limited 1979-2012
**Notes:** N/A
**File Name:** CRD endnote RIS n=3.txt

15.
**Database:** PROSPERO
**Host:** http://www.york.ac.uk/inst/crd/index.htm

**Data Parameters:** Feb 2011-Current
**Date Searched:** Monday, October 22nd 2012
**Hits:** 1
**Strategy:**

**(C peptide)**

**Limits:** N/A
**Notes:** N/A
**File Name:** Prospero

**Supplementary References**


1. Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013;**30**(7):803-17 doi: 10.1111/dme.12159[published Online First: Epub Date]|.
2. Cisse A, Chevenne D, Chauffert M, et al. [Contribution of plasma C-peptide to the classification of sugar diabetes in Dakar, Senegal]. Dakar medical 1997;**42**(1):11-4
3. Besser RE, Shepherd MH, McDonald TJ, et al. Urinary C-peptide creatinine ratio is a practical outpatient tool for identifying hepatocyte nuclear factor 1-{alpha}/hepatocyte nuclear factor 4-{alpha} maturity-onset diabetes of the young from long-duration type 1 diabetes. Diabetes Care 2011;**34**(2):286-91 doi: 10.2337/dc10-1293[published Online First: Epub Date]|.
4. Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). The DCCT Research Group. The Journal of clinical endocrinology and metabolism 1987;**65**(1):30-6 doi: 10.1210/jcem-65-1-30[published Online First: Epub Date]|.
5. Madsbad S, Faber OK, Binder C, et al. Prevalence of residual beta-cell function in insulin-dependent diabetics in relation to age at onset and duration of diabetes. Diabetes 1978;**27 Suppl 1**:262-4
6. Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. The Journal of clinical endocrinology and metabolism 2003;**88**(11):5090-8 doi: 10.1210/jc.2003-030180[published Online First: Epub Date]|.
7. Besser RE, Ludvigsson J, Jones AG, et al. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care 2011;**34**(3):607-9 doi: 10.2337/dc10-2114[published Online First: Epub Date]|.
8. Jones AG, Besser RE, McDonald TJ, et al. Urine C-peptide creatinine ratio is an alternative to stimulated serum C-peptide measurement in late-onset, insulin-treated diabetes. Diabet Med 2011;**28**(9):1034-8 doi: 10.1111/j.1464-5491.2011.03272.x[published Online First: Epub Date]|.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Supp |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7/Supp p1 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 1<br>7 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8/Fig 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Supp Table 1 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | Supp Table 2 & 3 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 10/Table 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | - |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | - |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 14 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 18 |

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

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