HbA1c, fasting plasma glucose and the prediction of diabetes: Inter99, AusDiab and D.E.S.I.R.

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ABSTRACT

INTRODUCTION: With diabetes defined by HbA1c≥6.5% &/or FPG≥7.0mmol/l &/or diabetes treatment, we investigated HbA1c and fasting plasma glucose (FPG) thresholds/change-points above which the incidence of diabetes increases.

METHODS: Data are Danish (Inter99), Australian (AusDiab) and French (D.E.S.I.R.), with respectively 4930, 6012 and 3784 non-diabetic participants.

RESULTS: Diabetes incidences at 5 years for Inter99 and AusDiab and at 6 years for D.E.S.I.R. were 2.3%, 3.1% and 2.4% respectively and incidences increased with baseline HbA1c and FPG. As HbA1c distributions differed between cohorts, HbA1c was standardized on D.E.S.I.R. data. Change-points where diabetes incidence increased were identified for HbA1c (%) after standardisation: 5.1(4.9-5.6) (Inter99), 5.4(5.1-5.6) (AusDiab), 5.3(5.1-5.7) (D.E.S.I.R.); for FPG change-points (mmol/l) were 5.1(...-6.1) (Inter99), 5.5(5.2-5.8) (AusDiab), no change-point for D.E.S.I.R.. Using current diabetes risk criteria HbA1c≥5.7% &/or FPG≥5.6mmol/l to screen for diabetes provided high sensitivity (over 89%) and positive predictive values: 4.3%, 6.9%.and 5.9% respectively.

CONCLUSIONS: HbA1c and FPG change-points predicting incident diabetes did not always exist, differed across studies, when available were generally lower than current criteria with wide confidence intervals. Using jointly HbA1c≥5.7% &/or FPG≥5.6mmol/l as a criterion for the risk of incident diabetes is appropriate.

Key words: diabetes, epidemiology, fasting plasma glucose, HbA1c.

Abbreviations: FPG, Fasting plasma glucose; IFG, Impaired fasting glucose; PPV, positive predictive value.

1. Introduction

Diabetes is a major public health problem globally and detecting those who have a high probability of developing type 2 diabetes is a priority, so that prevention programs can be proposed to people at greatest risk [1]. Indeed, throughout the world the number of people with diabetes is projected to increase to 439 million in 2030 from 285 million in 2010 [2].

Several studies have tried to characterise those with a high risk of developing diabetes using HbA1c, fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) following an oral glucose tolerance test (OGTT) [3,4]. FPG is the least expensive of these three measures of glycaemia, but it does require that individuals are fasting. An OGTT is time-consuming and more expensive. An advantage of HbA1c is that individuals need not be fasting [5]. Although HbA1c can be distorted by some diseases such as iron deficiency anaemia [6], the assay has several advantages such as a low intra-individual variability in non-diabetic people,[7] and the International Federation for Clinical Chemistry (IFCC) now has a method to standardize this assay, in order to overcome some of the differences between laboratories [8, 9].

Three hyperglycaemic states have been defined to indicate a risk of diabetes: HbA1c between 5.7 and 6.4%, impaired fasting glucose (IFG, FPG between 5.6 and 6.9 mmol/l) and impaired glucose tolerance (IGT, 2hPG between 7.8 and 11.0 mmol/l) [10]. In 2009, an Expert Committee indicated that people with an HbA1c between 6.0% and 6.4% were at risk for diabetes [11]; the 6.0% threshold was later lowered in the American Diabetes Association (ADA) recommendations to 5.7% in 2010 [10]. The lower limit of IFG was decreased in 2003 from 6.1 to 5.6 mmol/l by an ADA International Expert Committee [12]. While there are a number of studies that show there is an increased risk of diabetes for those with IGT and IFG [13], there has not been a search for more precise thresholds for these categories, nor for HbA1c. Indeed, the 2003 change in the definition of IFG has been disputed [14]. The oral glucose tolerance test is rarely used in clinical practice and we define diabetes in this article by either FPG ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5%, as this combination is likely to be used in clinical practice, as proposed in other publications [15, 16]. However, we have also included diabetes defined additionally by 2hPG ≥ 11.1 mmol/l, to evaluate possible changes in FPG and HbA1c thresholds.

We use epidemiologic studies from three countries: Denmark, Australia and France, the prospective cohorts: Inter99, AusDiab (Australian Diabetes, Obesity and Lifestyle Study) and

D.E.S.I.R. (Data from an Epidemiological Study on the Insulin Resistance syndrome) to determine whether there are thresholds or change-points for HbA1c, FPG and 2hPG, above which the incidence of diabetes increases at a significantly higher rate than below this change-point. Thresholds are characterised by their sensitivity, specificity, positive and negative predictive values for incident type 2 diabetes.

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2. Materials and methods

Inter99 is a Danish longitudinal study set up to evaluate whether individual intervention on life style factors (smoking, physical activity and unhealthy diet) can prevent cardiovascular disease and type 2 diabetes [17]. In 1999-2001, 13,016 individuals, 30-60 years, were randomly selected from the civil register in south western Copenhagen County, after stratification on age and sex [17]. Of the 6,906 who participated at the baseline examination, 122 were excluded: 99 for the language barrier and 23 for abuse of drugs or alcohol [17]. Among the 6784 eligible subjects (53% participation), 5228 attended the follow-up exam at five years. We excluded from our analyses: treated diabetic patients at baseline (64 were on insulin or oral drugs), those with missing HbA1c at baseline (n=5), missing FPG at baseline (n=23) or at follow-up respectively (n=30 then n=7). At baseline, 169 participants had diabetes defined by FPG ≥ 7.0 mmol/l and/or HbA1c after standardisation ≥ 6.5% and they have also been excluded. We analysed data from the 4930 participants without diabetes at baseline. When 2hPG was additionally studied, 4592 individuals were followed. HbA1c was assayed by ion-exchange high performance liquid chromatography technique (Bio-Rad variant) and values were DCCT-UKPDS aligned. Plasma venous glucose were assayed by the hexokinase/G6PD method (Boehringer Mannheim) [17]. Baseline body mass index (BMI) was evaluated in lightly clad participants.

AusDiab included 11,247 participants in 1999-2000 [18]. The selection of households was made by cluster sampling, stratified on the six States and the Northern Territory of Australia, and six census collectors' districts were randomly selected in each stratum; 17,129 households were eligible but only 11,479 responded to the interview, 11,247 individuals underwent biomedical examinations and 10,916 were eligible [18]. In 2004-2005, five years after inclusion, 6537 of the eligible subjects participated in the follow-up [19]. For analyses, among the 6378 non-diabetic subjects (159 had diabetes treatment), we excluded 44 subjects with missing HbA1c at baseline then 77 with missing HbA1c at follow-up;

There was no missing data for FPG at baseline and among remaining subjects, we deleted 46 with missing FPG at follow-up. We studied the 6012 non-diabetic participants aged between 25 and 88 years (199 participants were identified as diabetic at baseline by FPG ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5% after standardisation). When diabetes was additionally defined by 2hPG, 5704 individuals were studied. The variables measured were the same as in Inter99, however, the techniques of glucose and HbA1c assays were different. HbA1c was obtained by determining total glycated hemoglobin with high-performance liquid chromatography (Bio-Rad VARIANT hemoglobin testing system) then an algorithm was used to provide standardized HbA1c [19]. FPG was measured by the glucose oxidase method at baseline and hexokinase method at follow-up [19]. BMI was evaluated at baseline.

D.E.S.I.R. is a prospective study on the insulin resistance syndrome [3]. From the 5212 volunteers who participated, 4111 subjects were followed six years. We excluded from analyses: treated diabetic patients at baseline (n=44) and subjects without information on treatment at baseline (n=9) or at follow-up (n=122). We deleted subjects with missing baseline HbA1c (n=7), missing baseline FPG (n=5), missing HbA1c then FPG at follow-up (n=56, n=9) and finally 75 participants with baseline FPG ≥ 7.0 mmol/l and/or baseline HbA1c ≥ 6.5%. We used baseline data from 3784 men and women aged between 30 and 65 years. In D.E.S.I.R. the 2hPG was not available. HbA1c was measured by High Performance liquid chromatography with Bio-Rad aligned to DCTT-UKPDS standards and FPG by an enzymatic method (glucose oxidase/ peroxydase) with a Technicon RA 1000 automated analyser (Bayer) or a Specific or a Delta (Konelab) [3]. BMI was also evaluated at baseline.

2.1. Definitions

Diabetes was defined at baseline and at follow-up by treatment for diabetes &/or FPG ≥ 7.0 mmol/l &/or HbA1c ≥ 6.5% (after standardization).

Three other definitions of diabetes were also used to evaluate the stability of the change-points:

1. treatment for diabetes &/or FPG ≥ 7.0 mmol/l;
2. treatment for diabetes &/or HbA1c ≥ 6.5% (after standardization);
3. treatment for diabetes &/or FPG ≥ 7.0 mmol/l &/or HbA1c ≥ 6.5%. (after standardization) &/or 2hPG ≥ 11.1 mmol/l.

2.2. Statistical Methods

For each study, the characteristics of participants who developed and did not develop diabetes are described and compared between studies, using a χ^2 test for categorical variables and mean age, BMI and glycaemic parameters were compared by ANOVA.

As the HbA1c distributions differed between cohorts (Fig. 1A), we standardized the HbA1c data from Inter99 and AusDiab according to HbA1c data from the D.E.S.I.R. study. The difference in mean HbA1c of Inter99 and AusDiab in reference to D.E.S.I.R. was estimated in a linear regression model adjusted on age, sex and BMI. We thus subtracted 0.36% at baseline and 0.23% at follow-up from all Inter99 HbA1c values and added 0.38% at baseline and 0.19% at follow-up to all AusDiab HbA1c values. For FPG and 2hPG the distributions were similar across cohorts (Fig. 1B for FPG, Fig 1C for 2hPG).

The incidences of diabetes, as defined by treatment &/or FPG &/or HbA1c, are presented graphically according to baseline HbA1c (before standardisation Fig 2A, after standardisation Fig 2B) and according to baseline FPG (Fig. 2C), and they were modelled by logistic regression. We sought change-points beyond which the incidence of diabetes increased significantly for FPG and HbA1c, in separate models, and then in the same model; the likelihoods of the change point-models were compared with the likelihoods of simple linear models, using the χ^2 distribution [20]. The 95% confidence intervals for the change-points were constructed by identifying the change-points corresponding to the 2.5% and 97.5% values of the χ^2 distribution.

The stability of the change-points was studied when diabetes was defined according to the three other definitions of diabetes given above; for the first two definitions, the baseline population included those without diabetes based on treatment &/or FPG &/or HbA1c; for the third definition, those with diabetes at baseline according to 2hPG were also excluded.

Lastly, we estimated the sensitivity, specificity, positive and negative predictive values of HbA1c and FPG for different thresholds when diabetes was defined by treatment for diabetes &/or FPG ≥ 7.0 mmol/l &/or HbA1c ≥ 6.5%.(after standardization).

The SAS software version 9.1.3 was used for statistical analyses.

3. Results

The observed mean HbA1c after standardization (%) (5.4±0.4 for Inter99, 5.5±0.3 for AusDiab, and 5.4±0.4 for D.E.S.I.R.) and FPG (mmol/l) (5.5±0.4, 5.4±0.5 and 5.3±0.5 respectively for the three cohorts) were both significantly different between cohorts ($p < 0.0001$). For each cohort, all studied baseline characteristics of those who developed diabetes and those who did not were significantly different ($p < 0.03$) (Table 1).

The incidences of diabetes were: 2.3% for Inter99, 3.1% for AusDiab both over 5 years and 2.4% for D.E.S.I.R. over 6 years with different percentages with diabetes screened by treatment, FPG alone, HbA1c alone or both HbA1c and FPG (Table 1). Incidences increased with increasing baseline HbA1c, but the actual incidence at any given value of HbA1c differed between cohorts (Fig. 2A). However, after HbA1c standardization, the diabetes incidence curves were more similar (Fig. 2B). Change-points were present at 5.1% (Inter99), 5.4% (AusDiab) and 5.3% (D.E.S.I.R.), with wide confidence intervals. The incidences of diabetes with respect to baseline FPG were low and constant up until about 5.5 mmol/l and then increased with increasing FPG (Fig. 2C). The change-points for FPG were different for each study (5.1, 5.5 mmol/l for Inter99 and AusDiab), again with wide confidence intervals, with no change-point for D.E.S.I.R..

When FPG and HbA1c (after standardization) were used in the same model, joint change-points were available in all three cohorts: 5.1% for HbA1c and 5.6 mmol/l for FPG in the Inter99 study, 5.4% for HbA1c and 5.5 mmol/l for FPG in the AusDiab cohort and 5.4% for HbA1c and 5.6 mmol/l for FPG in D.E.S.I.R..

The HbA1c change-point for predicting diabetes by the four definitions did not change in D.E.S.I.R. (5.3%) (Table 2); for AusDiab, the definition of diabetes by FPG or by FPG &/or HbA1c provided the same change-points (5.4%) for HbA1c, but there was a much higher change-point for the HbA1c definition (6.4%). For Inter99, the change points varied from 5.1 to 5.9%. In AusDiab, the FPG change-point for predicting incident diabetes was the same whatever the diabetes definition (5.5 mmol/l); there were many cases for the two other cohorts when no change-point was detected. In particular, when the diabetes definition included 2hPG, the HbA1c changes points increased for both Inter99 and AusDiab, but for FPG, the change point was higher for Inter99, identical for AusDiab. For 2hPG a threshold of 9.9 mmol/l was found in AusDiab, but no change-point was detected in Inter99.

Test characteristics are shown for different thresholds of both FPG and HbA1c, when diabetes was defined by treatment &/or FPG &/or HbA1c (Table 3). For the currently proposed HbA1c threshold for diabetes risk of 5.7% [10], the positive predictive values were respectively 5.9% for Inter99, 11% for AusDiab and 7.6% for D.E.S.I.R.; for the FPG threshold of 5.6 mmol/l, the positive predictive values were respectively 4.8%, for Inter99, 7.6%,.for AusDiab and 7.3% for D.E.S.I.R..

For the combination of these two thresholds currently used individually as indicators for a risk for diabetes: HbA1c ≥ 5.7% **&** FPG ≥ 5.6 mmol/l, the sensitivity, specificity, positive and negative predictive values were: 54%, 87%, 8.6% and 99% for Inter99, 68%, 89%, 16% and 99% for AusDiab and 52%, 92%, 14% and 99% for D.E.S.I.R.; when we used the condition: HbA1c ≥ 5.7% **&/or** FPG ≥ 5.6 mmol/l, these values were respectively: 94%, 50%, 4.3% and 100% for Inter99, 93%, 60%, 6.9% and 100% for AusDiab and 89%, 65%, 5.9% and 100% for D.E.S.I.R.. Positive predictive values were lower for this second combination of thresholds than for the first combination.

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4. Discussion

We found change-points above which the incidence of diabetes began to increase significantly in Inter99 (for HbA1c at 5.5% before and 5.1% after standardization; for FPG at 5.1 mmol/l), in AusDiab (for HbA1c at 5.9% before and 5.4% after standardisation; for FPG at 5.5 mmol/l) and D.E.S.I.R (for HbA1c at 5.3%, no change-point detected for FPG). Change-points for FPG and HbA1c in the same model were 5.1% for HbA1c and 5.6 mmol/l for FPG for Inter99, 5.4% and 5.5 mmol/l respectively for AusDiab and 5.4% and 5.6 mmol/l respectively for D.E.S.I.R..

Positive predictive values showed a similar increase for all three cohorts, with a three to four fold increase for an HbA1c of 6.0% in comparison to 5.5% and a two to three fold increase for FPG at 6.0 mmol/l in comparison to 5.5 mmol/l. Positive predictive values for predicting diabetes were higher when we used both HbA1c & FPG than when we used HbA1c &/or FPG. Thus while the change-point method identified thresholds where the incidences increased, the absolute increase in positive predictive values at these points was not large. The negative predictive values were always close to 100%, while sensitivity was always higher than specificity for the currently recommended thresholds for hyperglycaemia of 5.6 mmol/l for FPG, while specificity was higher than sensitivity for HbA1c at 5.7%.

We explored separately data from three large studies (Danish, Australian and French) with a monitoring period of at least five years: the follow-up period was the same for Inter99 and AusDiab (5 years), one year more for D.E.S.I.R. (6 years). Among the limitations of our study, Inter99 is population-based, with a 53% acceptance to participate at baseline and two thirds were then followed; in AusDiab, 55% of invited participants underwent a biomedical examination at baseline, and then 58% of these were followed [19]; the D.E.S.I.R. cohort is not population-based, but 70% of the participants were able to be followed. There were differences in the three cohorts between those followed and not-followed, for at least one of the characteristics: gender, age, HbA1c, FPG, 2hPG or BMI, thus the studied population differed from that at inclusion (data not shown), however these differences while statistically significant, were minor. Another limitation is that the assay techniques used to measure HbA1c and plasma glucose were not the same in the three studies. All three HbA1c assays were DCCT-UKPDS aligned but as the distributions of HbA1c differed between the three cohorts, we standardised HbA1c measures on the D.E.S.I.R. study, after taking into account the age, sex and BMI differences in the three cohorts. Thus we are assuming that the basic distribution of HbA1c is identical in all three populations, after taking into account age, sex and BMI, and that the observed differences between HbA1c distributions were due to differences in the assays.

Other published studies have also analysed HbA1c and incident diabetes. Edelman et al. found that diabetes incidence was 2.5% per year for HbA1c between 5.6% and 6.0% [21]. The Expert Committee defined individuals with an HbA1c between 6.0% and 6.5% as being at high risk of diabetes [11]; subsequently, in January 2010 a new threshold of 5.7% was published in the ADA recommendations [10]. A recent study of Caucasian Europeans proposed that the most appropriate cut-point, using receiver operating characteristic (ROC) curves for the identification of IFG or IGT, was 5.8% [22]. The limits found by the change-point method in our analyses were lower (5.1% in Inter99, 5.4% in AusDiab and 5.3% in D.E.S.I.R.). Indeed, a systematic review has also indicated that there was a relationship between HbA1c and incident diabetes for HbA1c values from 5% [23] and Nakagami et al. found using a ROC curve that the optimal cut point for HbA1c in the prediction of incident diabetes over 5 years was at 5.1%, according to the Japan Diabetes Society HbA1c standardization, that is equivalent to 5.4% when aligned with the National Glycoprotein Standardization Program standardization [24]. However, the positive predictive values for the prediction of diabetes in our analyses double when baseline HbA1c increases from 5.0 to 5.5%, and

treble or quadruple between 5.5 and 6.0%, an exponential increase. For the prediction of diabetic complications, a different threshold might be recommended.

For FPG, change-points were at 5.1 mmol/l for Inter99 and 5.5 mmol/l for AusDiab with no change-point in D.E.S.I.R.. The Expert Committee published in the 2003 follow-up report, that the threshold values to predict diabetes found in Dutch, Pima Indian, Mauritius and San Antonio populations, were respectively: 5.7 mmol/l, 5.4 mmol/l, 5.4 mmol/l and 5.2 mmol/l using again, the criteria of maximizing sensitivity and specificity [25]. In our three studies, the 6.0 mmol/l threshold had a two to three fold higher positive predictive value than 5.5 mmol/l, whereas the positive predictive values for lower FPG values were similar.

We have not studied the 'optimum' thresholds, from sensitivity and specificity analyses; this maximisation is inappropriate as in screening for diabetes, and identifying those at risk of diabetes, the sensitivity is more important than the specificity. The change-point method provided different values in the three populations, and the confidence intervals were very wide. We believe that the positive predictive value may be the more appropriate metric to identify thresholds. Even though the positive predictive value is dependent on the basic incidence of diabetes in each population, it increased similarly for all cohorts, for both parameters: HbA1c and FPG.

Inoe et al. [26] analysed data from 10 042 Japanese men and women with a follow-up period of 5.5 years and baseline FPG < 7.0 mmol/l; they found that the cumulative incidence of diabetes was more than 2.0% for HbA1c between 5.5% and 6.4%. The use of HbA1c would have allowed the identification of people with a higher diabetes risk that would not have been detected by FPG alone. The 5.5% threshold was close to the change-points that we found (5.4% for AusDiab, 5.3% for D.E.S.I.R.). Inoue et al. also sought the cumulative incidence of diabetes among subjects with IFG who had HbA1c between 5.5% and 6.4%; it was 25%, higher than the cumulative incidence in those with IFG and HbA1c <5.5% (7.6%) [26].

Other studies analysed HbA1c according to ethnicity. The Third National Health and Nutrition Examination Survey data the U.S. found that the distribution of HbA1c differed between races; the mean HbA1c for non-treated individuals was higher in black non-Hispanic than in Mexican-Americans and lower in non-Hispanic whites [27].

We have previously studied incident diabetes, where diabetes was defined by treatment and/or HbA1c ≥ 6.5% [28]. In strictly non-diabetic subjects, those with HbA1c < 6.5% and

FPG < 7.0 mmol/l and no treatment for diabetes, HbA1c was able to predict incident diabetes, defined by HbA1c ≥ 6.5% and/or treatment, with an area under the receiver operating characteristic curve of 0.84, 0.91 and 0.82 for Inter99, AusDiab and D.E.S.I.R. respectively, indicating that HbA1c was able to discriminate incident diabetes as defined by HbA1c [28].

For HbA1c, while the three studies showed similar incidence curves, the HbA1c distributions differed considerably. The need for standardization of the HbA1c assay, so that it is more closely aligned to the DCCT-UKPDS standard, and better to the IFCC standard, is necessary if HbA1c is to be used as a diagnostic criterion for diabetes. The ADA recommendation states explicitly that the HbA1c assay should be standardized [8,9].

In conclusion, our results show that both HbA1c and FPG predict diabetes, defined on the basis of treatment and/or high glucose and/or high HbA1c values, with similar incidence curves. Even after standardisation of HbA1c, there were differing change-points in the three studies for HbA1c and equally for FPG, as well as differences according to the definition of diabetes. Change-points were lower than the thresholds proposed to define hyperglycemic states by the World Health Organisation and the American Diabetes Association, and they had large confidence intervals. The current thresholds of 5.7% for HbA1c and 5.6 mmol/L for FPG appear adequate, and if either one or the other occurs, the positive predictive values for incident diabetes corresponds to approximately twice the incidence of diabetes in the background population.

Conflict of interest

KBJ holds stock shares in Novo Nordisk.

DW and DV are employed by Steno Diabetes Center A/S, a research and teaching hospital working in the Danish National Health Service and owned by Novo Nordisk A/S. DW and DV hold stock shares in Novo Nordisk A/S.

The other authors declare no conflict of interest.

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AusDiab

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D.E.S.I.R.

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REFERENCES

[1] Narayan KM, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of recent increase in incidence on future diabetes burden: U.S., 2005-2050. Diabetes Care, 2006;29:2114-6.

[2] Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract, 2010;87:4-14.

[3] Droumaguet C, Balkau B, Simon D, Caces E, Tichet J, Charles MA et al. Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care, 2006;29:1619-25.

[4] Abdul-Ghani MA, Lyssenko V, Tuomi T, DeFronzo RA, Groop L. Fasting versus postload plasma glucose concentration and the risk for future type 2 diabetes: results from the Botnia Study. Diabetes Care, 2009;32:281-6.

[5] American Diabetes Association. Screening for type 2 diabetes. Diabetes Care, 2004;27 (Suppl. 1):S11-4.

[6] Kim C, Bullard KM, Herman WH, Beckles GL. Association between iron deficiency and A1C Levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999-2006. Diabetes Care, 2010;33:780-5.

[7] Borch-Johnsen K, Colagiuri S. Diagnosing diabetes--time for a change? Diabetologia, 2009;52:2247-50.

[8] Consensus committee. Consensus statement on the worldwide standardization of the hemoglobin A1C measurement: the American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation. Diabetes Care, 2007;30:2399-400.

[9] Hanas R, John G. 2010 consensus statement on the worldwide standardization of the hemoglobin A(1c) measurement. Diabetes Res Clin Pract, 2010;90:228-30.

[10] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2010;33 (Suppl. 1):S62-9.

[11] International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 2009;32:1327-34.

[12] Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.

Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care, 2003;26 (Suppl 1):S5-20.

[13] Borch-Johnsen K, Colagiuri S, Balkau B, Glumer C, Carstensen B, Ramachandran A et al. Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. Diabetologia, 2004;47:1396-402.

[14] Dekker JM, Balkau B. Counterpoint: impaired fasting glucose: The case against the new American Diabetes Association guidelines. Diabetes Care, 2006;29:1173-5.

[15] Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G et al. Combined measurement of fasting plasma glucose and A1C is effective for the prediction of type 2 diabetes: the Kansai Healthcare Study. Diabetes Care, 2009;32:644-6.

[16] Cederberg H, Saukkonen T, Laakso M, Jokelainen J, Härkönen P, Timonen M et al. Postchallenge glucose, A1C, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: A 10-year prospective cohort study. Diabetes Care, 2010; 33:2077-83.

[17] Glumer C, Jorgensen T, Borch-Johnsen K. Inter99 study. Prevalences of diabetes and impaired glucose regulation in a Danish population: the Inter99 study. Diabetes Care, 2003;26:2335-40.

[18] Dunstan DW, Zimmet PZ, Welborn TA, Cameron AJ, Shaw J, de Courten M et al. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab)--methods and response rates. Diabetes Res Clin Pract,, 2002;57:119-29.

[19] Magliano DJ, Barr EL, Zimmet PZ, Cameron AJ, Dunstan DW, Colagiuri S et al. Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. Diabetes Care, 2008;31:267-72.

[20] Ulm K. A statistical method for assessing a threshold in epidemiological studies. Stat. Med., 1991;10:341-9.

[21] Edelman D, Olsen MK, Dudley TK, Harris AC, Oddone EZ. Utility of hemoglobin A1c in predicting diabetes risk. J. Gen. Intern. Med., 2004;19:1175-80**.**

[22] Mostafa SA, Khunti K, Srinivasan BT, Webb D, Gray LJ, Davies MJ. The potential impact and optimal cut-points of using glycated haemoglobin, HbA1c, to detect people with impaired glucose regulation in a UK multi-ethnic cohort. Diabetes Res. Clin. Pract., 2010;90:100-8.

[23] Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care, 2010;33:1665-73.

[24] Nakagami T, Tajima N, Oizumi T, Karasawa S, Wada K, Kameda W et al. Hemoglobin A1c in predicting progression to diabetes. Diabetes Res Clin Pract., 2010;87:126-31.

[25] Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care, 2003;26:3160-7.

[26] Inoue K, Matsumoto M, Akimoto K. Fasting plasma glucose and HbA1c as risk factors for Type 2 diabetes. Diabet. Med., 2008;25:1157-63.

[27] Saaddine JB, Fagot-Campagna A, Rolka D, Narayan KM, Geiss L, Eberhardt M et al. Distribution of HbA(1c) levels for children and young adults in the U.S.: Third National Health and Nutrition Examination Survey. Diabetes Care, 2002;25:1326-30.

[28] Soulimane S, Simon D, Shaw JE, Zimmet PZ, Vol S, Vistisen D et al. Comparing incident diabetes as defined by fasting plasma glucose or by HbA1c. The AusDiab, Inter99 and D.E.S.I.R. studies. Diabetic Medicine in press

FIGURE LEGENDS

Fig. 1— The distribution of A. HbA1c, B. fasting plasma glucose (FPG) and C. 2 hour plasma glucose (2hPG) at baseline, in the three cohorts, AusDiab, Inter99 and D.E.S.I.R.. The population studied was those followed-up, not treated for diabetes at baseline and without missing data for FPG and HbA1c : 4930 individuals for Inter99, 6012 for AusDiab, 3784 for D.E.S.I.R.. For 2hPG there are 4592 individuals for Inter99 and 5704 for AusDiab.

Fig. 2— Incident diabetes (%), in the three studies: Inter99, AusDiab, D.E.S.I.R.. Diabetes is defined by treatment &/or fasting plasma glucose (FPG) $\geq$ 7.0 mmol/l and/or HbA1c $\geq$ 6.5%. The curves show the predicted incidence of diabetes at follow up from logistic regression models, the points show the observed incidences, according to baseline values of HbA1c (A: before HbA1c standardisation, B: after HbA1c standardisation) and FPG (C). The *p* values for the presence of a change-point where the slope of the relation changes and the change-points (95% CI), are given.

Table 1—Description of incident diabetes n (%) according to screening method; baseline characteristics (mean ± SD, n (%)), according to incident diabetes status. Inter99 (followed 5 years), AusDiab (followed 5 years), and D.E.S.I.R. (followed 6 years), with diabetes defined by treatment for diabetes and/or fasting plasma glucose ≥ 7.0 mmol/l &/or HbA1c ≥ 6.5%.

	Inter99 N=4930			AusDiab N=6012			D.E.S.I.R. N=3784		
	No incident diabetes n=4816	Incident diabetes n=114 (2.3%)	*P* value	No incident diabetes n=5826	Incident diabetes n=186 (3.1%)	*P* value	No incident diabetes n=3692	Incident diabetes n=92 (2.4%)	*P* value
Treatment for diabetes (%)		16 (0.3)			55 (0.9)			25 (0.7)	
FPG ≥ 7mmol/l alone (%)		59 (1.2)			71 (1.2)			27 (0.7)	
HbA1c ≥ 6.5% alone (%)		20 (0.4)			15 (0.3)			18 (0.4)	
FPG ≥ 7mmol/l & HbA1c ≥ 6.5% (%)		19 (0.4)			45 (0.7)			22 (0.6)	
Age (years)	46 ± 8	50 ± 6	<.0001	51 ± 13	56 ± 12	<.0001	47 ± 10	52 ± 9	<.0001
Men (%)	2348(48.7)	77(67.5)	<.0001	2566(44.0)	96(51.6)	0.03	1776(48.1)	63(68.5)	<.0001
HbA1c before standardisation (%)[†]	5.7 ± 0.3	6.1 ± 0.3	<.0001	5.1 ± 0.3	5.5 ± 0.3	<.0001	5.4 ± 0.4	5.8 ± 0.4	<.0001
HbA1c after standardisation (%)	5.4 ± 0.4	5.8 ± 0.4	<.0001	5.5 ± 0.3	5.9 ± 0.3	<.0001	5.4 ± 0.4	5.8 ± 0.4	<.0001
Fasting plasma glucose (mmol/l)	5.4 ± 0.5	6.1 ± 0.5	<.0001	5.3 ± 0.5	6.1 ± 0.6	<.0001	5.2 ± 0.5	6.0 ± 0.5	<.0001
2 hour plasma glucose (mmol/l)									
BMI (kg/m²)	26.0 ± 4.3	30.1 ± 4.8	<.0001	26.5 ± 4.6	30.6 ± 5.7	<.0001	24.5 ± 3.5	28.7 ±4.8	<.0001

[†]Based on 4703 participants for Inter99 (with 132 (2.8%) with incident diabetes), 6025 for AusDiab (186 (3.1%) with incident diabetes) and 3784 for D.E.S.I.R. (92 (2.4%) with incident diabetes). The numbers studied changed after HbA1c standardisation as different individuals were included/excluded by the 6.5% HbA1c threshold.

Table 2—Change-points (95% CI) for HbA1c and FPG when diabetes was screened by treatment and by either or both of HbA1c and fasting plasma glucose (FPG), or additionally by 2 hour plasma glucose (2hPG) in the Inter99 and AusDiab studies

	Inter99	*P**	AusDiab	*P*	D.E.S.I.R.	*P*
HbA1c predicting diabetes defined by						
Treatment &/or FPG &/or HbA1c	5.1 (4.9-5.6)	<0.0001	5.4 (5.1-5.6)	0.003	5.3 (5.1-5.7)	0.0007
Treatment &/or HbA1c	No threshold	0.13	6.4 (6.2-6.5)	<0.0001	5.3 (4.8-5.5)	0.001
Treatment &/or FPG	5.1 (4.8-5.5)	<0.0001	5.4 (5.1-5.6)	0.004	5.3 (5.0-5.7)	0.001
Treatment &/or FPG &/or HbA1c &/or 2hPG †	5.9 (5.0-6.2)	0.0001	5.6 (5.1-6.1)	0.02		
Fasting plasma glucose predicting diabetes defined by						
Treatment &/or FPG &/or HbA1c	5.1 (... – 6.1)	0.03	5.5 (5.2-5.8)	<0.0001	No threshold	0.10
Treatment &/or HbA1c	No threshold	0.15	5.5 (5.2-6.1)	0.001	No threshold	0.06
Treatment &/or FPG	No threshold	0.22	5.5 (5.1-5.7)	<0.0001	No threshold	0.08
Treatment &/or FPG &/or HbA1c &/or 2hPG †	5.7 (4.3-6.9)	0.049	5.5 (4.8-6.2)	<0.0001		
2 hour plasma glucose predicting diabetes defined by						
Treatment &/or FPG &/or HbA1c&/or 2hPG †	No threshold	0.17	9.9 (7.7-10.8)	0.04		

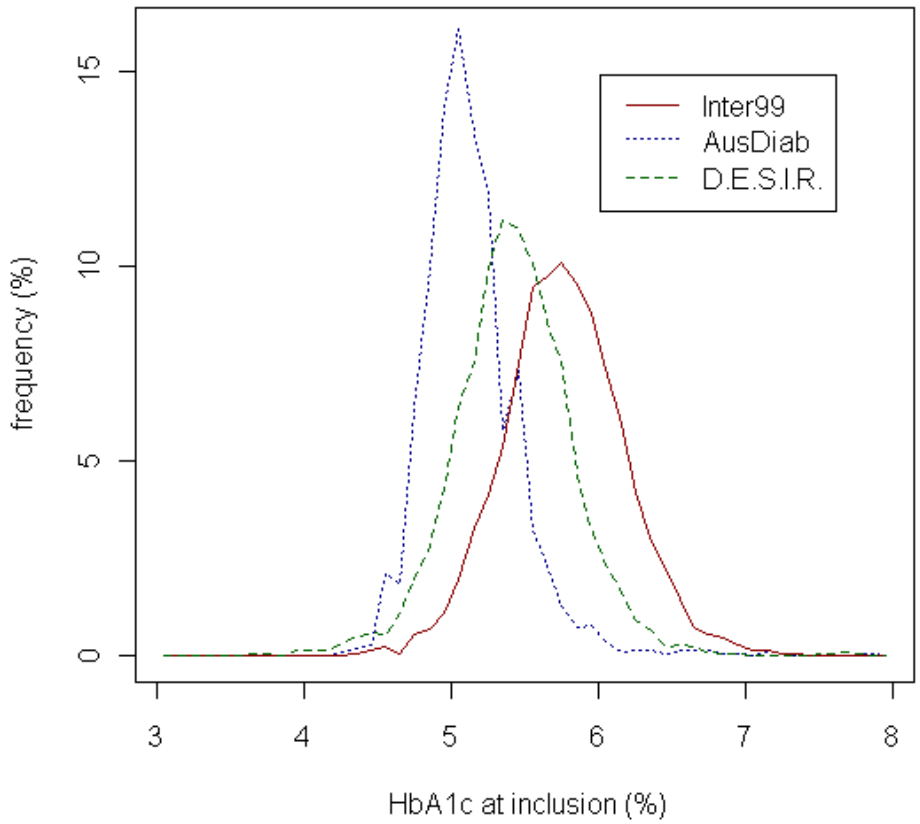
* *P* value indicates whether the model with a change-point was better than a simple linear model without a threshold, using a χ^2 likelihood ratio test

†Based on 4592 individuals in Inter99 and 5704 in AusDiab. The numbers studied differ from those in other analyses because of missing data for 2hPG at baseline and at follow-up, and because individuals with diabetes defined by 2hPG at baseline were excluded

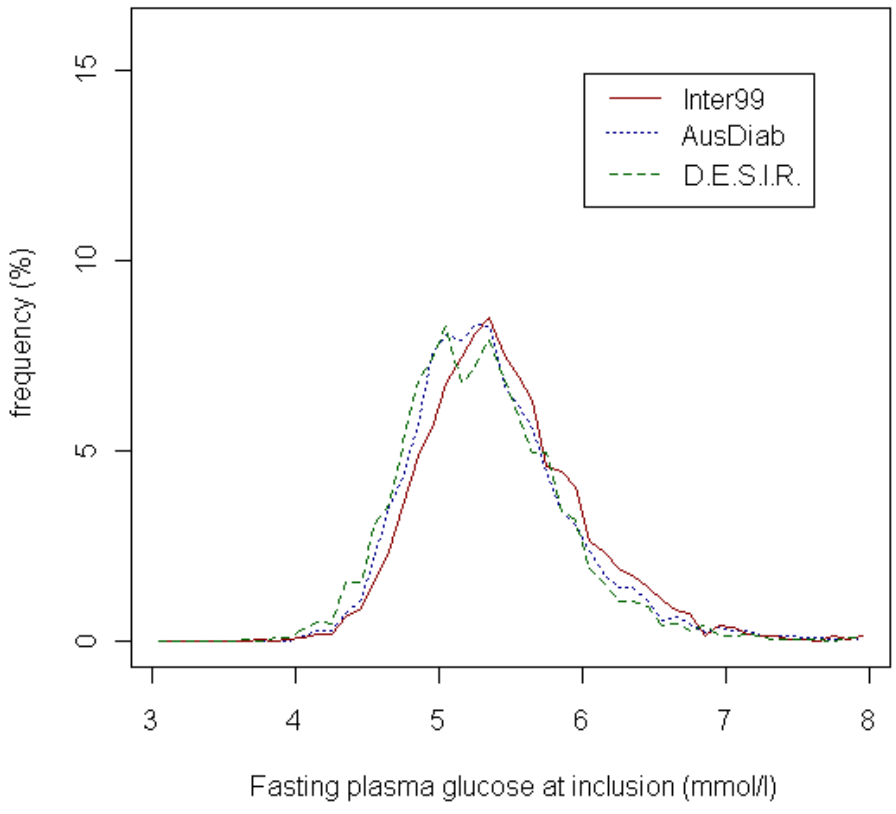
Table 3—Sensitivity (%), specificity (%), positive predictive values (%), negative predictive values (%) for incident diabetes defined by treatment &/or FPG &/or HbA1c, for various thresholds of HbA1c (after standardization) and fasting plasma glucose (FPG).

	Sensitivity (%)						*Specificity (%)*						*Positive Predictive Value (%)*						*Negative Predictive Value (%)*					
HbA1c (%)	*5.0*	*5.5*	*5.7*	*6.0*	*6.4*		*5.0*	*5.5*	*5.7*	*6.0*	*6.4*		*5.0*	*5.5*	*5.7*	*6.0*	*6.4*		*5.0*	*5.5*	*5.7*	*6.0*	*6.4*	
Inter99	95	80	65	42	6.1		13	57	76	93	100		2.5	4.2	5.9	13	29		99	99	99	99	98	
AusDiab	99	88	78	45	2.1		3.1	59	81	96	100		3.2	6.3	11	28	27		99	99	99	98	97	
D.E.S.I.R.	96	80	66	38	4.3		13	61	80	95	100		2.7	4.9	7.6	17	44		99	99	99	98	98	
FPG (mmol/l)	*5.0*	*5.5*	*5.6*	*6.0*	*6.5*	*6.8*	*5.0*	*5.5*	*5.6*	*6.0*	*6.5*	*6.8*	*5.0*	*5.5*	*5.6*	*6.0*	*6.5*	*6.8*	*5.0*	*5.5*	*5.6*	*6.0*	*6.5*	*6.8*
Inter99	97	87	83	70	32	12	15	54	61	84	97	99	2.6	4.2	4.8	9.6	18	34	99	99	99	99	98	98
AusDiab	95	83	82	65	34	11	19	61	68	89	98	100	3.6	6.4	7.6	15	36	54	99	99	99	99	98	97
D.E.S.I.R.	94	75	75	55	17	7.6	32	70	76	93	99	100	3.3	5.9	7.3	17	28	39	99	99	99	99	98	98

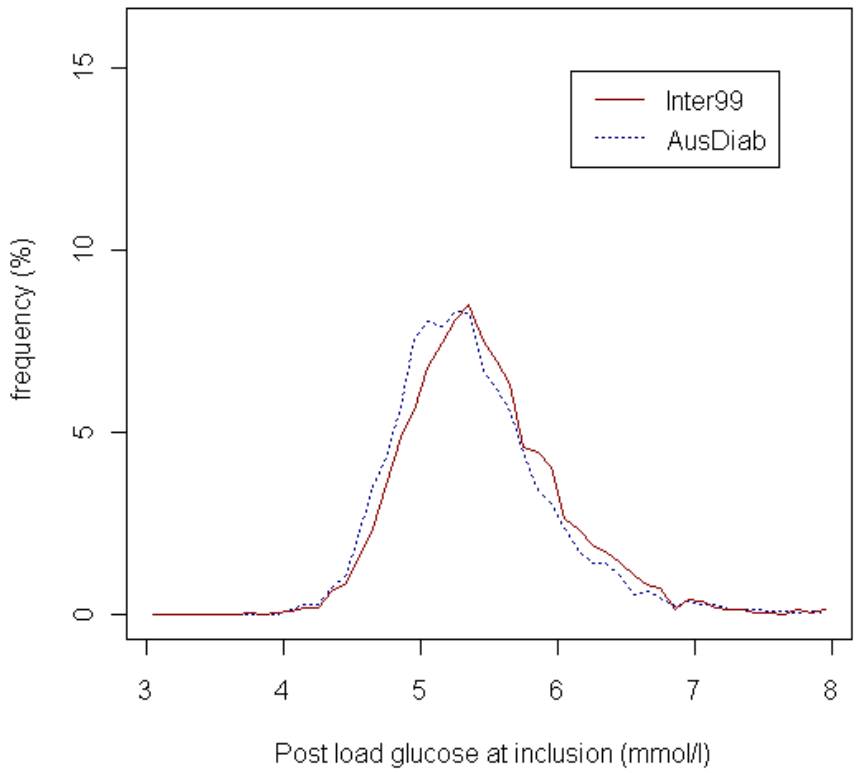
A

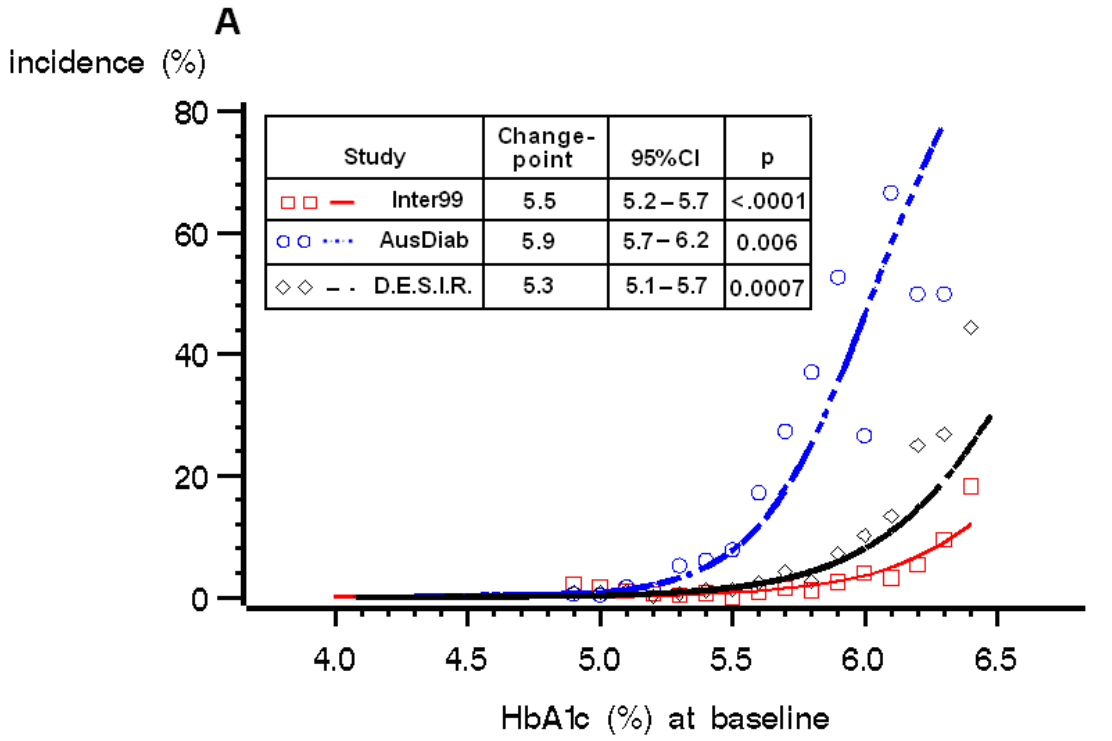

Inter99
AusDiab
D.E.S.I.R.
frequency (%)
0
5
10
15
3
4
5
6
7
8
HbA1c at inclusion (%)

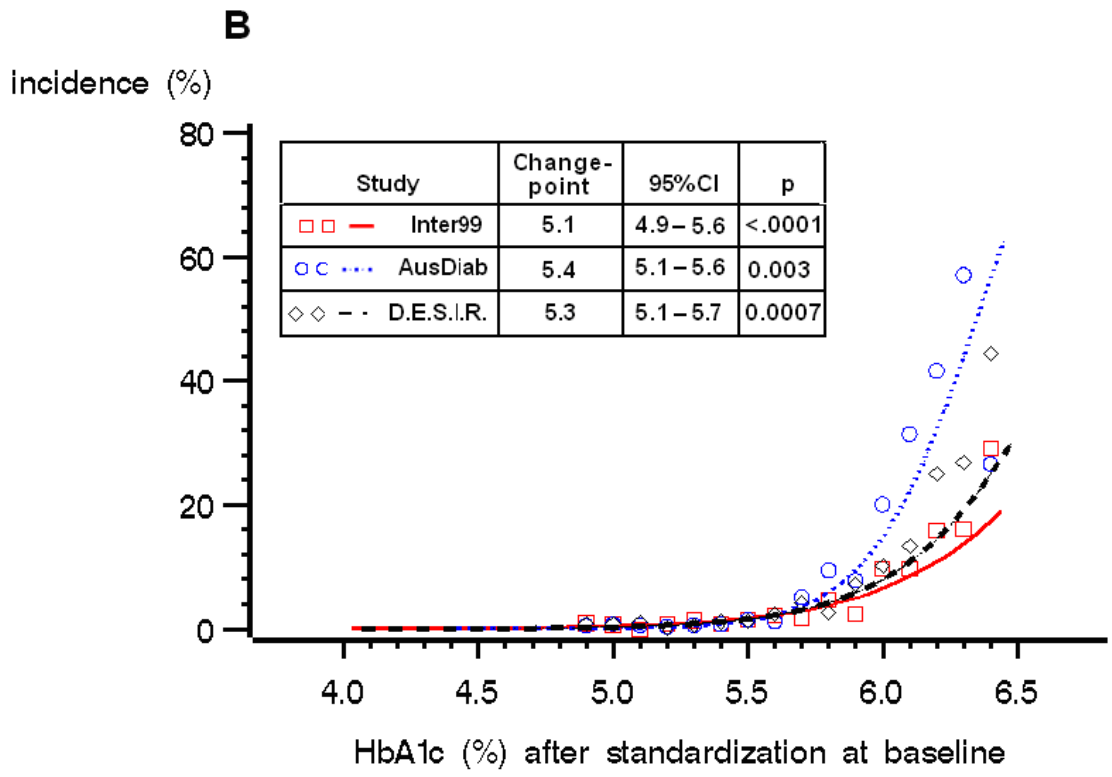
B

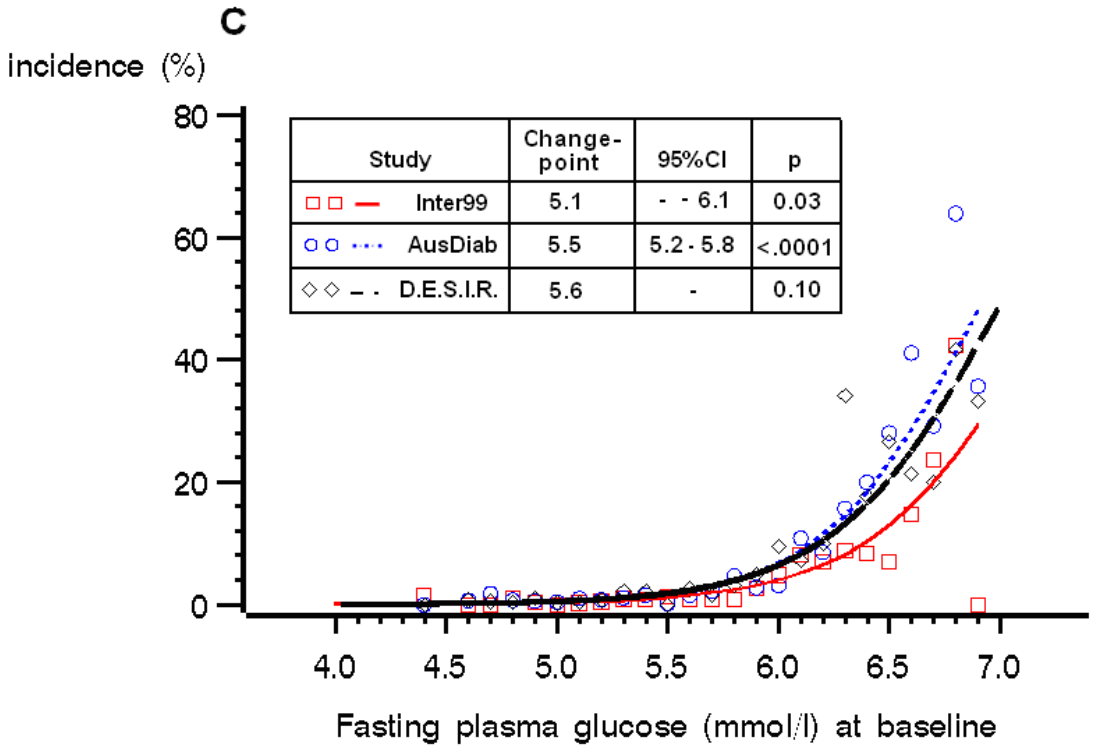

Inter99
AusDiab
D.E.S.I.R.
frequency (%)
0
5
10
15
3
4
5
6
7
8
Fasting plasma glucose at inclusion (mmol/l)

C


Inter99
AusDiab
frequency (%)
0
5
10
15
3
4
5
6
7
8
Post load glucose at inclusion (mmol/l)


A
incidence (%)
Study
Change-point
95%CI
p
Inter99
5.5
5.2 – 5.7
<.0001
AusDiab
5.9
5.7 – 6.2
0.006
D.E.S.I.R.
5.3
5.1 – 5.7
0.0007
80
60
40
20
0
4.0
4.5
5.0
5.5
6.0
6.5
HbA1c (%) at baseline


B
incidence (%)
Study
Change-point
95%CI
p
Inter99
5.1
4.9 – 5.6
<.0001
AusDiab
5.4
5.1 – 5.6
0.003
D.E.S.I.R.
5.3
5.1 – 5.7
0.0007
80
60
40
20
0
4.0
4.5
5.0
5.5
6.0
6.5
HbA1c (%) after standardization at baseline


C
incidence (%)
80
60
40
20
0
Study
Change-point
95%CI
p
Inter99
5.1
- - 6.1
0.03
AusDiab
5.5
5.2 - 5.8
<.0001
D.E.S.I.R.
5.6
-
0.10
4.0
4.5
5.0
5.5
6.0
6.5
7.0
Fasting plasma glucose (mmol/l) at baseline