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Comparing incident diabetes as defined by fasting plasma glucose or by HbA1c. The AusDiab, Inter99 and D.E.S.I.R. studies

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Aim We examine the ability of fasting plasma glucose (FPG) and HbA1c to predict 5 year incident diabetes for an Australian and a Danish cohort and 6 year incident diabetes for a French cohort, as defined by the corresponding criteria.

Methods 6025 men and women from AusDiab (Australian), 4703 from Inter99 (Danish) and 3784 from D.E.S.I.R. (French), not treated for diabetes and with FPG<7.0mmol/l and HbA1c<6.5% (48 mmol/mol) at inclusion, were studied. Diabetes was defined as FPG≥7.0mmol/l and/or treatment for diabetes or as HbA1c≥6.5% (48mmol/mol) and/or treatment for diabetes.

Results For AusDiab, incident FPG–defined diabetes was more frequent than HbA1c-defined diabetes ($P_{McNemar}$<0.0001), the reverse applied to Inter99 ($P_{McNemar}$<0.007), and for D.E.S.I.R. there was no difference (P_{McNema}=0.17). Fewer than one third of the incident cases were detected by both criteria. Logistic regression models showed that baseline FPG and baseline HbA1c predicted incident diabetes defined by the corresponding criteria. The standardized odds ratios [95% confidence interval] for HbA1c were a little higher than for FPG, but not significantly so. They were respectively, 5.0 [4.1-6.1] and 4.1 [3.5-4.9] for AusDiab, 5.0 [3.6-6.8] and 4.8 [3.6-6.3] for Inter99, 4.8 [3.6-6.5] and 4.6 [3.6-5.9] for D.E.S.I.R..

Conclusions FPG and HbA1c are good predictors of incident diabetes defined by the corresponding criteria. Despite DCCT-alignment of the three HbA1c assays, there was a large difference in the HbA1c distributions between these studies, conducted some ten years ago. Thus it is difficult to compare absolute values of diabetes prevalences and incidences based on HbA1c from that time.

Key words FPG, HbA1c, incident diabetes

Abbreviations AUC, area under the curve; DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; IFCC, International Federation of Clinical Chemistry; IFG, impaired fasting glucose; ROC, receiver operating characteristic.

Introduction

The prevalence of diabetes in adults, aged 20 to 79 years, is projected to increase worldwide from 6.4% in 2010 to 7.7% in 2030 [1]. It is important to detect individuals with diabetes to start treatment and to detect those at high risk of diabetes, to initiate strategies to prevent or delay its occurrence, as interventions to control and to prevent diabetes have been shown to be cost-effective [2].

In the 1980s, the World Health Organization examined, and rejected, the possibility of using HbA1c in the diagnosis of diabetes [3]. International expert committees have subsequently proposed a role for HbA1c: a first report published in January 2003, cited results showing that macro- and micro-vascular complications of diabetes increased significantly above certain HbA1c thresholds [4]; in a follow-up report in November 2003, the American Diabetes Association committee presented the advantages of HbA1c, but also the problems of assay standardization [5]. Since then, the International Federation of Clinical Chemistry (IFCC) has developed a new reference method for the standardization of HbA1c assays in reference laboratories [6]. HbA1c has recently been recommended for the diagnosis of diabetes by an international expert group and also for the identification of those at risk of diabetes [7]. The American Diabetes Association currently recommends the use of HbA1c as one of four criteria for diagnosing diabetes [8].

Several groups have already published results on the prediction of incident diabetes using fasting plasma glucose (FPG) and HbA1c, in those without known diabetes [9,10], where diabetes was defined by treatment and/or FPG $\geq$ 7.0 mmol/l. They have shown that various combinations of FPG and HbA1c levels improve the detection of subjects with a high risk of developing diabetes, and that they predict diabetes better than either FPG or HbA1c alone [9,10]. Nakagami et al. showed that FPG and HbA1c had similar areas under the curve (AUC) of the receiver operating characteristic (ROC) curves, for discriminating those with and without incident diabetes, defined using both FPG and the 2-hour plasma glucose after an oral glucose challenge [11].

Thus, to date, studies have addressed the question of comparing FPG with HbA1c in relation to their use as risk factors for glucose-based diagnosis of diabetes. However, if we switch to using HbA1c for diagnosis, we need to know if HbA1c-diagnosed diabetes can be predicted by baseline

HbA1c, and to compare this with glucose-diagnosed diabetes as predicted from fasting glucose at baseline.

This work compares diabetes incidence according to two definitions of diabetes: 1) FPG ≥ 7.0 mmol/l and/or diabetes treatment and 2) HbA1c ≥ 6.5% (48 mmol/mol) and/or diabetes treatment in three studies: AusDiab, Inter99 (5 years follow-up) and D.E.S.I.R. (6 years follow-up).

Study population

Study population

In each of the three cohorts, we excluded all participants with missing data for FPG or HbA1c or diabetes treatment by drugs, either at baseline or at follow-up. For the study of incident diabetes we further excluded participants with baseline FPG ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5% (48 mmol/mol) at baseline.

AusDiab

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) aimed to describe the prevalence and risk factors of diabetes in Australia [12]. In 1999-2000, adults aged ≥ 25 years, and resident for at least 6 months at the same address, were included from all eligible households sampled by cluster; census collector districts (on average 225 houses) were randomly selected, with six clusters in each of seven strata (six States and the Northern Territory) [12]. Of the 20 347 eligible subjects who completed a household questionnaire, 11 247 had a biomedical exam at inclusion (55% participation) [12] and among the 10,788 participants eligible for testing in 2004–2005, 6,537 (60%) participated and another 2,261 (21%) completed a telephone questionnaire only. Thus, the response rate for the follow-up was 61% (6,537 of 10,788). [13]. We excluded those treated by drugs at baseline for known diabetes (n=159), participants with missing HbA1c at baseline (n=44) and at follow-up (n=77) and among remaining participants, those with missing FPG at follow-up (n=46). For the study of incident diabetes, we also excluded individuals with baseline HbA1c ≥ 6.5% (48 mmol/mol) (n=72); then those with FPG at baseline ≥ 7.0 mmol/l (n=114): 6025 individuals were studied.

FPG was assayed by the glucose oxidase method at baseline (automated analyzer Olympus AU600) and by the hexokinase method at follow-up (Roche modular analytics system) [15]. HbA1c was determined from total glycated hemoglobin (GHb) measured by DCCT aligned high performance liquid chromatography, using ion-exchange methodology (Bio-Rad variant hemoglobin testing system Bio-Rad, Hercules, CA, USA) [12,13]. Height and weight were measured without shoes or heavy clothes.

Inter99

As part of a prevention program for cardiovascular disease and type 2 diabetes, 12 934 men and women aged between 30 and 60 years, were randomly selected in 1999-2001 from vital records registers (civil registration of the population) of 11 Copenhagen municipalities, in Denmark [14]. Sampling was stratified by age and sex. Participation in the study was 53% and 6784 participants were included after exclusion of 23 for heavy alcohol or drug consumption and 99 for poor understanding of the language [14]; 5228 (77%) individuals were followed five years later. We excluded all those treated by drugs at baseline for known diabetes (n=64). We excluded participants in the same manner as for AusDiab: missing HbA1c at baseline (n=5), missing HbA1c at follow-up (n=31), missing FPG at baseline (n=22), missing FPG at follow-up (n=7), thus the study population included 5099 participants. For the study of incident diabetes we also excluded: those whose baseline HbA1c $\geq$ 6.5% (48 mmol/mol) (n=347), then those with FPG $\geq$ 7.0 mmol/l (n=49), leaving 4703 individuals for analysis.

FPG was measured by the hexokinase method and HbA1c by DCCT aligned ion-exchange high-performance liquid chromatography [15]; participants wore underwear and no shoes for weight and height measurement [16].

D.E.S.I.R.

The French cohort study Data on the Epidemiology of the Insulin Resistant syndrome (D.E.S.I.R.) included 5212 volunteers, men and women aged 30-65 years, consulting at periodic health examinations in nine French Departments, in 1994-1996 [17]. Participant inclusion was stratified by

age and sex. An examination was conducted every 3 years, over 9 years, but we considered only the 6 year follow-up examination so that follow-up time was similar to the two other cohorts; 4111 participants attended the 6-year follow-up visit. We excluded at baseline, individuals treated by drugs for diabetes (n=44), and those without information on diabetic treatment (n=9). At follow-up, there were 122 participants with missing data on treatment. We also excluded those with missing HbA1c at baseline (n=7), with missing HbA1c at follow-up (n=56), missing FPG at baseline (n=5) and missing FPG at follow-up (n=9), leaving 3859 participants. For the study of incident diabetes, we excluded those with baseline HbA1c ≥ 6.5% (48 mmol/mol) (n=48), then those with baseline FPG ≥ 7.0 mmol/l (n=27): 3784 subjects were studied.

FPG was measured by the glucose oxidase method (Technicon RA 1000 analyzer or Specific or Delta from Konelab) and HbA1c was standardized to a DCCT aligned high-performance liquid chromatography (L9100 automated ion exchange analyzer). Subjects were weighed and measured without shoes, in light clothing [17].

Statistical analysis

Anthropometric characteristics and laboratory measures as well as baseline diabetes prevalences are presented as mean ± SD or n (%), by study cohort, and cohorts are compared by ANOVA or χ^2 tests.

The number of incident cases of diabetes was determined at 5 years for Inter99 and AusDiab and at 6 years in D.E.S.I.R., according to the two definitions of diabetes: 1) FPG ≥ 7.0 mmol/l and/or treatment for diabetes and 2) HbA1c ≥ 6.5% (48 mmol/mol) and/or treatment for diabetes, and logistic regression models were used to predict incident diabetes according to either the FPG or HbA1c definitions, in the individual studies. Model adequacy was evaluated by the Hosmer-Lemeshow test [18] where the individuals are divided into groups of equal size (ten or eleven) according to centiles of predicted probabilities, and the numbers in these groups observed and estimated from the model are compared with the χ^2 distribution. The AUC of the ROC curve was used as measure of discrimination between those who did and did not develop diabetes [18].

For each cohort, the odds ratios for an increase in one SD of baseline FPG and HbA1c to predict diabetes, defined on the corresponding criteria, were used to compare the strengths of these

predictions. The differences in these standardized odds ratios were compared by bootstrap sampling, with 1000 repetitions, sampling the same numbers of individuals as in each cohort.

Finally, the frequencies of incident diabetes, as defined by the two criteria, FPG and HbA1c, were determined in each cohort, and compared by the McNemar test.

The baseline distributions of HbA1c differed markedly between the three cohorts, (Table 1, Figure 1B). After adjusting for age, sex and BMI, the mean HbA1c was -0.38% (-4.2 mmol/mol) lower for AusDiab and ±0.36% (3.9 mmol/mol) higher for Inter99 in comparison with D.E.S.I.R.; in contrast, for FPG these differences were much smaller: 0.02 and 0.16 mmol/l respectively. At follow-up the mean HbA1c was -0.17% (-1.9 mmol/mol) lower for AusDiab and 0.22% (2.4 mmol/mol) higher for Inter99, compared to D.E.S.I.R.. Therefore, in a supplementary analysis, we adjusted the HbA1c distributions at baseline and at follow up by adding or subtracting the appropriate constant, assuming that the basic distribution of HbA1c was identical in the three cohorts, using successively, each cohort as the reference cohort. These results are presented in the Supplementary Results (on line).

Statistical analyses used SAS software (version 9.2) and R (version 2.10).

Results

Participant characteristics differed between the three cohorts, with significant differences in mean ages of 3.9 years between AusDiab and D.E.S.I.R. and 4.7 years between AusDiab and Inter99 (Table 1); BMI was highest in AusDiab and 2.3 kg/m² lower in D.E.S.I.R.. FPG was highest in Inter99 and lowest in D.E.S.I.R. with a mean difference of 0.2 mmol/l (Table 1, Figure 1A). Inter99 had a mean HbA1c of 5.8% (40 mmol/mol), almost two SD higher than AusDiab which had a mean HbA1c of 5.1% (32 mmol/mol). (Table 1, Figure 1B). The prevalences of diabetes screened by FPG differed by a factor of two between cohorts, but for HbA1c-screened diabetes, there was a six-fold difference between Inter99 with a prevalence of 6.8% and the 1.2% prevalences of both AusDiab and D.E.S.I.R..

The overall incidence of diabetes was 3.1% in AusDiab, 2.8% in Inter99 and 2.4% in D.E.S.I.R. if the combined criteria of treatment and/or FPG ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5% (48 mmol/mol) were used (Table 2). The percentage of incident cases treated for diabetes varied between

studies, from 0.3% in Inter99, to 0.6% in D.E.S.I.R., to 0.8% in AusDiab (Table 2). The incidence of screened diabetes differed significantly between the FPG and HbA1c definitions of diabetes: AusDiab 2.0% for FPG and 0.8% for HbA1c ($P_{McNemar}$<.0001); Inter99 1.2% for FPG and 1.7% for HbA1c ($P_{McNemar}$=0.007) but not for D.E.S.I.R.: 1.3% for FPG and 1.1% for HbA1c ($P_{McNemar}$=0.17) (Table 2). However, combining all three cohorts, the incidence of diabetes was higher by FPG than by HbA1c: 1.6% and 1.2% respectively ($P_{McNemar}$=0.0005). It should be noted that FPG and HbA1c identified different individuals with diabetes, with overall only one quarter being identified by both criteria (Table 2).

The incidences of diabetes as defined by FPG and/or treatment for diabetes, increased with increasing baseline FPG (Figure 2A), for all three cohorts. The AUCs [95% CIs] of the ROC curves for FPG were 0.84 [0.81-0.88] for AusDiab, 0.86 [0.83-0.91] for Inter99 and 0.86 [0.82-0.92] for D.E.S.I.R.. The logistic models fitted the observed data adequately according to the Hosmer-Lemeshow test, better in AusDiab and Inter99 than in D.E.S.I.R. with $P_{Hosmer\text{-}Lemeshow}$=0.34, 0.54 and 0.05 respectively. The incidence of diabetes in all three studies increased from a FPG around 5.7 mmol/l, with a very low incidence of diabetes for lower values of FPG.

For diabetes defined by HbA1c and/or treatment for diabetes, there was also a good discrimination with AUCs [95% CIs] of 0.91 [0.89-0.95], 0.81 [0.78-0.86] and 0.84 [0.79-0.90] for AusDiab, Inter99, and D.E.S.I.R. respectively. The incidence was modeled adequately for the three cohorts ($P_{Hosmer\text{-}Lemeshow}$=0.47, 0.19 and 0.57 respectively).

For AusDiab, the standardized odds ratio [95% CI] for developing diabetes by one SD increase in FPG was 4.1 [3.5-4.9], and for HbA1c 5.0 [4.1-6.1]; for Inter99 the corresponding odds ratios were 4.8 [3.6-6.3] and 5.0 [3.6-6.8] and for D.E.S.I.R., 4.6 [3.6-6.0] and 4.8 [3.6-6.5]. Bootstrap sampling showed that there was no statistically significant difference between the odds ratios for FPG- and HbA1c-defined diabetes, in any of the cohorts.

After adjusting HbA1c, so that the mean HbA1c (age and sex adjusted) in all three cohorts was identical, the incidences of diabetes varied considerably according to the cohort on which HbA1c was adjusted (Supplementary Table 1), both for FPG-defined diabetes and for HbA1c-defined diabetes. In most cases, diabetes incidence by FPG and by HbA1c differed significantly. For all

HbA1c adjustments, the incidence curves increased with increasing FPG and HbA1c (Supplementary Figures 1A, 1B, 1C, 1D) and were more spread out for HbA1c when adjusted on AusDiab and tighter when adjusted on Inter99. While the standardized odds ratios for predicting FPG-defined and HbA1c-defined diabetes, changed according to the reference cohort (Supplementary Table 2), HbA1c had a higher standardized odds ratio than FPG in seven of the nine cases, but this was only significantly higher in two cases. With comparable HbA1c values, we were able to combine the three cohorts, to compare the overall odds ratio for FPG and HbA1c; for the Inter99 and D.E.S.I.R. adjusted data, the odds ratio associated with HbA1c-defined diabetes was significantly higher than the odds-ratios associated with FPG-defined diabetes; this was not the case for AusDiab adjusted data.

Discussion

In all three cohorts, FPG at baseline predicted incident diabetes, defined by FPG (and/or treatment for diabetes) and HbA1c at baseline predicted incident diabetes defined by HbA1c (and/or treatment for diabetes) with a good fit, as shown by non-significant Hosmer-Lemeshow tests. The discrimination was also good for both criteria, with AUCs above 0.81 in all three studies, for both baseline FPG and baseline HbA1c, for incident diabetes defined on the corresponding criteria, distinguishing those who developed diabetes from those who did not. Despite the fact that screening and treatment for diabetes is mainly based on FPG and hence FPG could have been expected to perform better, the difference in odds ratios between FPG and HbA1c defined diabetes was not statistically significant in any of the three cohorts. When we adjusted the HbA1c data successively on each of the three cohorts, and combined data across cohorts, the odds ratios for HbA1c were significantly higher than for FPG in two of the three adjustments.

There were significant differences between the percentages of incident cases of diabetes identified by FPG or by HbA1c for AusDiab and Inter99, with more diabetes cases by FPG for AusDiab and more diabetes cases by HbA1c for Inter99; combining all three cohorts, the percentage with incident diabetes was higher for FPG. Only one quarter of those identified by one or other method were identified by both.

Kramer et al. [19] found in a cross-sectional study, that more than 85% of those found to have an HbA1c ≥ 6.5% (48 mmol/mol) did not have diabetes based on fasting and/or two hour glucose levels, and that one-third who had diabetes based on glucose levels had HbA1c < 6.5% (48 mmol/mol). In our three incident cohorts, AusDiab, Inter99 and D.E.S.I.R., 21%, 75% and 45% of participants identified as having diabetes by HbA1c did not have diabetes by FPG (Table 2), and 69%, 63% and 55% with diabetes by FPG had HbA1c < 6.5% (48 mmol/mol) (Table 2). As in the Rancho Bernardo Study, the two parameters (FPG and HbA1c) were not always high together in our three cohorts. In Inter99, the mean HbA1c was 5.8% (41 mmol/mol) in those with diabetes on FPG alone, thus many of them would have been considered at high risk based on their HbA1c. The corresponding mean was 5.6% (38 mmol/mol) in D.E.S.I.R. and 5.4% (36 mmol/mol) in AusDiab but in the latter study, the HbA1c average at baseline in untreated subjects was very low (5.1%, 33 mmol/mol).

Our results show that HbA1c is a good marker for the detection of people at high risk of developing incident diabetes defined by HbA1c. In the D.E.S.I.R. study, Droumaguet et al. [17] showed that both FPG and HbA1c can detect people who develop incident diabetes, where diabetes was defined according to the FPG definition: from a ROC curve analysis, maximizing the sum of the sensitivity and specificity, for individuals with IFG (FPG 6.1-6.9 mmol/l) a threshold of 5.9% (41 mmol/mol) for HbA1c had a 64% sensitivity and 77% specificity for 6-year incident diabetes. A recent publication from the Atherosclerosis Risk in Communities (ARIC) study [20] showed that HbA1c was associated with a risk of 13-year incident diabetes, where diabetes was defined by FPG ≥ 7.0 mmol/l, physician diagnosis or treatment.

When international alignment of HbA1c assays is achieved, results obtained by HbA1c should be more consistent than those from FPG, as intra-individual variability is lower for HbA1c than for FPG [8], even if two measures are always required for diagnosis. HbA1c has the additional advantage that individuals need not be fasting: we can never be certain that all subjects were fasting when the blood was taken to measure FPG [8].

The results of the HbA1c assay can be influenced by assay method and by the presence of certain conditions. Indeed, in some hereditary illnesses such as sickle cell disease, the result may be falsely high, and during bleeding or haemolysis the HbA1c result can be lowered [21]. A recent

publication showed that iron deficiency could influence the HbA1c assay by giving higher values when HbA1c < 6.0% (42 mmol/mol) [22]. In subjects suffering from conditions that could affect the HbA1c level, the use of a glucose test is recommended [7]. Ethnic differences in the relation between HbA1c and glucose have been shown for individuals from Greenland and from the Inter99 study: Caucasians from Denmark had a lower HbA1c for a given glucose level [23]; HbA1c assays were from the same laboratory for both studies.

The strengths of our study are the long follow-up (at least five years) and the size of the cohorts. Indeed, the total number followed in the three populations was close to 15 000. The main limitation of our study is the lack of one central laboratory and additionally the different assay methods between the three cohorts. Follow-up was also different between studies, with six years in D.E.S.I.R. and five years in the two other cohorts. However, despite this, the D.E.S.I.R. study does seem to have a lower diabetes incidence or prevalence than the other two studies. Screening was based on a single blood sample: in clinical practice, two results are needed for diagnosis, either by FPG or by HbA1c [7]. The 2 hour glucose from the oral glucose tolerance test has not been used in this analysis, as we aimed to describe results relevant to clinical practice, where this test is rarely used.

In conclusion, FPG and HbA1c can identify individuals who will develop diabetes, based on the corresponding FPG and HbA1c criteria, in all three cohorts. The incidence of diabetes started to increase after an FPG of approximately 5.7 mmol/l. For HbA1c using the original data from each cohort, the thresholds where incidence increased differed widely by study – around 5.4% (36 mmol/mol) for AusDiab, 5.9% (41 mmol/mol) for D.E.S.I.R. and 6.1% (39 mmol/mol) for Inter99, reflecting the different mean HbA1c levels at both baseline and follow-up in these three cohorts. Indeed, the threshold of 5.7% (43 mmol/mol) for HbA1c has been proposed as being associated with an increased risk of diabetes in the American Diabetes Association report [8], and equally 5.6 mmol/l has been proposed for the definition of impaired fasting glucose [8]. However, with our study, the differing HbA1c distributions between the three cohorts clearly demonstrates the problems of comparing data based on older assays, even if they were DCCT standardized. It is to be expected that HbA1c distributions will be able to be compared between populations with more precision once the IFCC quality control is applied in reference laboratories. The long-term complications of diabetes

related with glucose and with HbA1c need to be studied, to determine which is the best measure of glycaemia to define diabetes.

Conflict of interest

DV is 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, and hold shares in Novo Nordisk. KBJ holds shares in Novo Nordisk. The other authors declare no conflict of interest.

Acknowledgments

AusDiab

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INTER99

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D.E.S.I.R.

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FIGURE LEGENDS

FIGURE 1 The distribution of **A.** fasting plasma glucose and **B.** HbA1c, at baseline, in the three cohorts, AusDiab, Inter99 and D.E.S.I.R.. The population studied was those followed-up, but not treated for diabetes at baseline.

FIGURE 2 Incident diabetes, in the three studies: AusDiab, Inter99 and D.E.S.I.R.. Diabetes was defined by **A.** fasting plasma glucose $\geq$ 7.0 mmol/l and/or diabetes treatment or **B.** HbA1c $\geq$ 6.5% (48 mmol/mol) and/or diabetes treatment. The curves represent the predicted probability of diabetes at follow-up from logistic regression models, and the symbols are the corresponding observed incidences. The risks associated with one SD increase in the variable were estimated by standardized ORs and their 95% confidence intervals: OR_{stand} (95% CI). The numbers of participants in each cohort for each observed incidence are shown.

Table **1** Baseline characteristics (mean ± SD, n (%)) of participants in the three studies, n=15 169, and values of HbA1c at follow-up.

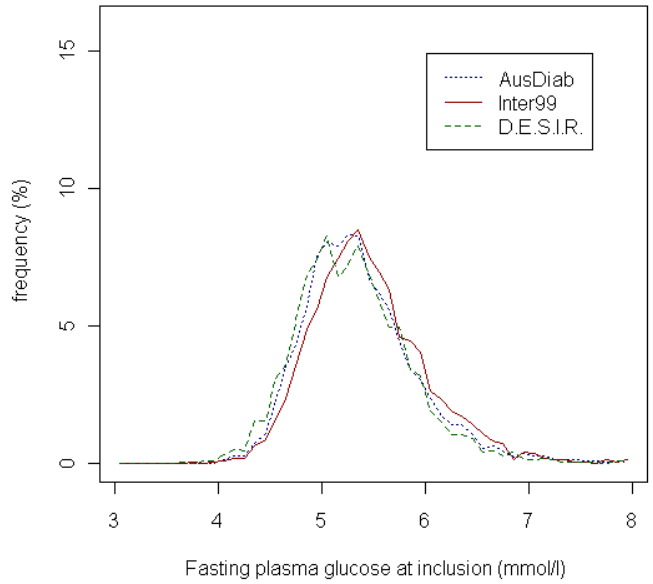
	AusDiab	**Inter99**	**D.E.S.I.R.**	***P***
Baseline, treated diabetes	**n=6370**	**n=5163**	**n=3903**	
	159(2.5%)	64(1.2%)	44(1.1%)	<.0001
Baseline, in those non treated for diabetes	**n=6211**	**n=5099**	**n=3859**	
Prevalent screened diabetes FPG ≥ 7.0 mmol/l	180(2.9%)	135(2.6%)	55(1.4%)	<.0001
Prevalent screened diabetes HbA1c ≥ 6.5% (48 mmol/mol)	72(1.2%)	347(6.8%)	48(1.2%)	<.0001
Men (%)	2778(45%)	2550(50%)	1890(49%)	<.0001
Age (years)	51.2 ± 12.7	46.5 ± 7.8	47.3 ± 9.9	<.0001
BMI (kg/m²)	26.8 ± 4.8	26.3 ± 4.5	24.5 ± 3.6	<.0001
FPG (mmol/l)	5.4 ± 0.7	5.5 ± 0.8	5.3 ± 0.6	<.0001
HbA1c				
(%)	5.1 ± 0.4	5.8 ± 0.5	5.4 ± 0.4	<.0001
(mmol/mol)	33 ± 4	40 ± 5	36 ± 4	
After follow-up, in those not diabetic at baseline and not treated for diabetes at follow-up	**n=5968**	**n=4691**	**n=3759**	
FPG (mmol/l)	5.4 ±0.5	5.4 ±0.5	5.3 ±0.5	<.0001
HbA1c				
(%)	5.4 ± 0.3	5.7 ± 0.3	5.5 ± 0.4	<.0001
(mmol/mol)	35 ± 4	39 ± 3	37 ± 4	

Table **2** Incident diabetes, defined by treatment, fasting plasma glucose and HbA1c, at 5 years for AusDiab and Inter99 and 6 years for D.E.S.I.R..

	AusDiab n=6025	**Inter99 n=4703**	**D.E.S.I.R. n=3784**
Treated incident diabetes patients	57 (0.9%)	12 (0.2%)	25 (0.7%)
Newly screened diabetes by			
Isolated-FPG*	82 (1.4%)	36 (0.8%)	27 (0.7%)
Isolated-HbA1c**	10 (0.2%)	63 (1.3%)	18 (0.5%)
Both FPG & HbA1c***	37 (0.6%)	21 (0.4%)	22 (0.6%)
	129 (2.1%)	120 (2.6%)	67 (1.8%)
Total with incident diabetes	186 (3.1%)	132 (2.8%)	92 (2.4%)

*Isolated-FPG: fasting plasma glucose ≥ 7.0 mmol/l and HbA1c < 6.5% (48 mmol/mol)
**Isolated-HbA1c: HbA1c ≥ 6.5% (48 mmol/mol) and fasting plasma glucose < 7.0 mmol/l
***Both FPG & HbA1c: fasting plasma glucose ≥ 7.0 mmol/l and HbA1c ≥ 6.5% (48 mmol/mol)

A



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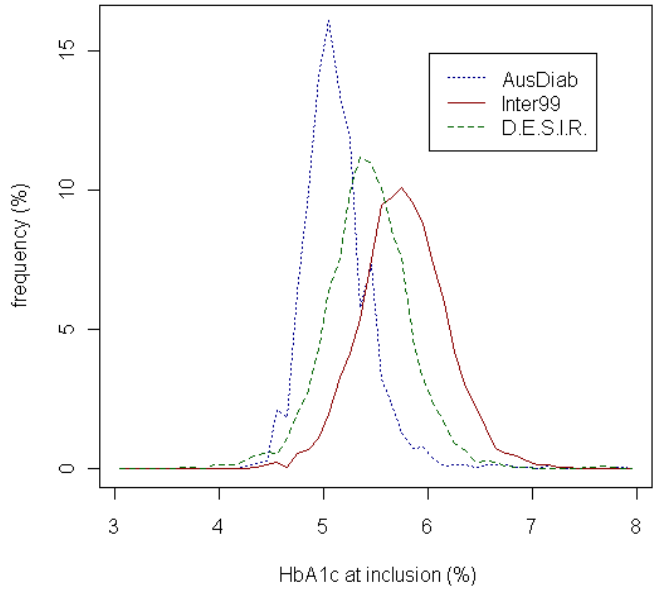

FIGURE 1 The distribution of **A.** fasting plasma glucose and **B.** HbA1c, at baseline, in the three cohorts, AusDiab, Inter99 and D.E.S.I.R.. The population studied was those followed-up, but not treated for diabetes at baseline.

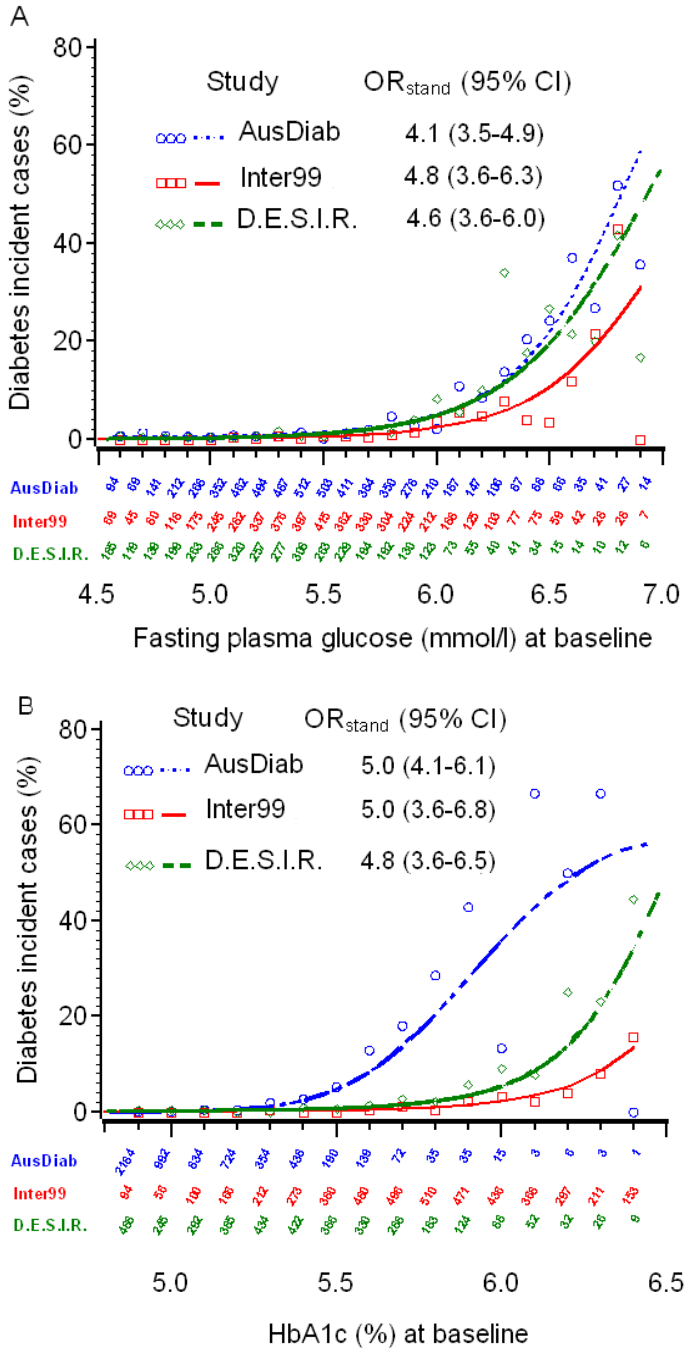

FIGURE 2 Incident diabetes, in the three studies: AusDiab, Inter99 and D.E.S.I.R.. Diabetes was defined by **A.** fasting plasma glucose ≥ 7.0 mmol/l and/or diabetes treatment or **B.** HbA1c ≥ 6.5% (48 mmol/mol) and/or diabetes treatment. The curves represent the predicted probability of diabetes at follow-up from logistic regression models, and the symbols are the corresponding observed incidences. The risks associated with one SD increase in the variable were estimated by standardized ORs and their 95% confidence intervals: OR_{stand} (95% CI). The numbers of participants in each cohort for each observed incidence are shown.