Associations between pre-diabetes, by three different diagnostic criteria, and incident CVD differ in South Asians and Europeans

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Abstract

Objective: We examined longitudinal associations between pre-diabetes and cardiovascular disease (CVD) (coronary heart disease (CHD) and stroke) in Europeans and South Asians.

Research design and methods: UK cohort study of 1,336 Europeans and 1,139 South Asians, aged 40-69 years at baseline (1988-91). Assessment included blood pressure, blood tests, anthropometry and questionnaires. Pre-diabetes was determined by OGTT or HbA_{1c}, using either International Expert Committee (IEC, HbA_{1c} 6.0-6.5% (42-48 mmol/mol)) or American Diabetes Association (ADA, HbA_{1c} 5.7-6.5% (39-48 mmol/mol)) cut-points. Incident CHD and stroke were established at 20 years from death certification, hospital admission, primary care record review and participant report.

Results: Compared to normoglycaemic individuals, IEC-defined pre-diabetes was related to both CHD and CVD risk in Europeans but not South Asians (sub-hazards ratio[95% CI]: CHD;1.68[1.19,2.37] vs. 0.99[0.74,1.33], ethnicity interaction p=0.008, CVD; 1.49[1.08,2.07] vs. 1.03[0.79,1.36], ethnicity interaction p=0.04). Conversely, IEC-defined pre-diabetes was associated with stroke risk in South Asians but not Europeans (1.75 [1.04,2.93] vs. 0.85[0.45,1.64], ethnicity interaction p=0.11). Risks were adjusted for age, sex, smoking, total/HDL-cholesterol ratio, waist/hip ratio, systolic blood pressure and anti-hypertensive use. . Associations were weaker for OGTT or ADA-defined pre-diabetes. Conversion from pre-diabetes to diabetes was greater in South Asians, but accounting for time to conversion did not account for these ethnic differences.

Conclusions: Associations between pre-diabetes and CVD differed by pre-diabetes diagnostic criterion, type of CVD and ethnicity, with associations being present for overall CVD in Europeans but not South Asians. Substantiation of these findings and investigation of potential explanations are required.

In parallel with the global diabetes epidemic, population surveys indicate an escalating prevalence of non-diabetic hyperglycaemia (12-29%, depending on definition)(1); hereon in referred to as "pre-diabetes". Historically, pre-diabetic states have been defined by either fasting (impaired fasting glycaemia [IFG]) or post-challenge (impaired glucose tolerance [IGT]) glycaemia(2), though recently HbA_{1c}-based definitions of pre-diabetes have been advocated(3, 4). Controversy exists regarding the role of pre-diabetes in cardiovascular disease (CVD) risk, particularly concerning whether pro-active identification and management are warranted(5).

Large prospective studies indicate that glycaemia (by glucose or HbA_{1c}) below the diabetic threshold is weakly related to CVD risk(6-8), and a recent Mendelian randomization study hinted at a limited causal role for dysglycaemia in coronary heart disease(9). However, studies examining the CVD consequences of pre-diabetes by specific diagnostic criteria are limited to European origin populations or focus on risk factors or mortality, rather than clinical disease(10-14). Host and migrant South Asian populations have a markedly greater prevalence of overt diabetes(15) and higher CVD rates than populations of European descent(16), yet associations between pre-diabetes and CVD have not been compared in these ethnic groups. Relatively more pre-diabetes is identified by HbA_{1c} than IFG/IGT criteria in people of South Asian origin, whereas prevalence is similar by either criterion in European origin populations(17). Therefore, it has been suggested that the HbA_{1c} definition of pre-diabetes may be a less discerning indicator of CVD risk in South Asians(18). However, our previous work suggests that diabetes is more strongly related to CVD risk in South Asians than Europeans(16, 19); whether similar ethnic differences exist for pre-diabetes remains unstudied.

Using data from a community-based cohort study, our objectives were: i) to examine longitudinal associations between pre-diabetes and CVD in UK Europeans and South Asians,

ii) to describe ethnic differences in these associations, and iii) to explore potential reasons for any ethnic differences.

Research design and methods

Study participants and design

The <u>S</u>outhall <u>A</u>nd <u>B</u>rent <u>Re</u>visited (SABRE) study is a community-based multi-ethnic cohort study of cardiometabolic disease; details are published elsewhere[20]. Participants aged 40-69 years at baseline (1988-1991, n=4857, 2346 European, 1710 South Asian and 801 African Caribbean) were randomly selected from primary care physician lists and workplaces in north-west London. South Asian participants were first-generation migrants originating from the Indian subcontinent, approximately half (52%) were of Punjabi Sikh origin. A male preponderance in the data exists as the baseline study was initially designed to examine cardiometabolic disease in men. Participants were followed for death, hospitalisation, and primary care consultations from baseline to 2011. All participants gave written informed consent. Approval for the baseline study was obtained from Ealing, Hounslow and Spelthorne, Parkside and University College London research ethics committees, and at follow-up from St. Mary's Hospital Local Research Ethics Committee (reference: 07/HO712/109).

Baseline measurements

Participants underwent blood tests, blood pressure and anthropometric measurement, and provided data on smoking, physical activity and occupation using previously validated questionnaires[21]. Fasting lipids, glucose and HbA_{1c} were measured as described[20, 22]. HbA_{1c} was measured (at baseline and follow-up) using an immunoassay on a clinically automated analyser (c311; Roche, Burgess Hill, UK), the high and low quality control

coefficients of variation were 2.9 and 3.3% respectively. Those whose diabetes status was unknown underwent oral glucose tolerance testing (OGTT). We used three classification systems to define glycaemic status for participants without existing diabetes. Firstly, World Health Organisation (WHO) 1999 criteria were used to define pre-diabetes (either impaired fasting glycaemia [fasting glucose$\geq$6.1 mmol/l and <7.0 mmol/l] or impaired glucose tolerance [2 hour oral glucose tolerance test plasma glucose$\geq$7.8 mmol/l and <11.1 mmol/l]) and new diabetes (fasting glucose$\geq$7.0mmol/l or 2 hour oral glucose tolerance test plasma glucose$\geq$11.1 mmol/l)(2). Secondly, glycaemic categories according to the International Expert Committee (IEC) 2009 criteria(3) were based on the following HbA$_{1c}$ cut-points: pre-diabetes; HbA$_{1c}$ $\geq$6.0% (42 mmol/mol) but <6.5% (48 mmol/mol), new diabetes HbA$_{1c}$ $\geq$6.5% (48 mmol/mol). We also studied glycaemia according to the American Diabetes Association (ADA) 2014 recommendations(4), which advocate HbA$_{1c}$ cut-points of $\geq$5.7% (39 mmol/mol) but <6.5% for pre-diabetes and $\geq$6.5% (as for IEC criteria) for new diabetes.

Smoking status was dichotomised as ever/ never smoked. Weekly frequency of fruit and vegetable consumption was assessed by food frequency questionnaire. Questions on physical activity provided a summary estimate of weekly energy expenditure in daily activities, walking and sport(23). Height was measured barefoot with a stadiometer, weight with calibrated weighing scales, waist circumference halfway between the costal margin and the iliac crest and hip circumference at the greater trochanter. Seated resting brachial blood pressure was measured using a random zero sphygmomanometer (Hawksley, London, United Kingdom); the mean of two measurements was used in analyses.

Follow-up measurements

Between 2008 and 2011, survivors were invited for examination at St. Mary's hospital, London. Incident coronary heart disease (CHD) was defined firstly from primary care record

review adjudicated by two clinicians – diagnosis was based on symptoms, cardiac enzymes, electrocardiography findings, exercise test findings and coronary revascularisation procedures, as per Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) criteria(24). Secondly, CHD was identified from Hospital Episode Statistics (HES) (ICD-9: 410-415, ICD-10: I200-I259) and data from the Office of Populations and Surveys classification of interventions and procedures (pertaining to coronary revascularisation interventions or rehabilitation for ischaemic heart disease, codes: K401-K469, K491-K504, K751-K759, U541). For stroke, primary care data were reviewed in a similar manner to CHD, with diagnoses made again according to ASCOT criteria, based on symptoms, duration of symptoms and magnetic resonance/ computer tomographic imaging(24). Stroke was also ascertained from participant report of physician-diagnosed stroke with duration of symptoms≥ 24 h and from Hospital Episode Statistics (ICD-9: 430-439, ICD-10: I600-I698). New cases of diabetes since baseline were identified from record review, questionnaire, clinic blood results, (using i) fasting and post OGTT load glucose results according to WHO 1999 criteria, or ii) $HbA_{1c} \geq 6.5\%$), or death certificate data (ICD-9: 2500-2509, ICD-10: E100-E149).

Statistical analysis

Baseline characteristics were compared by follow-up status and ethnicity. Logistic and linear regression methods determined age- and sex-adjusted differences. Using age- and sex-adjusted Cox models, we compared rates of incident CHD, stroke and CVD (CHD + stroke) by ethnicity and studied numbers of events by glycaemic categories and ethnicity. Age- and sex-adjusted associations between pre-diabetes (defined in three ways, as above) or new/ known diabetes and CHD, stroke and CVD were examined in each ethnic group (model 1). We then further adjusted these models for potential a priori-specified confounders, comprising CVD risk factors (smoking, total/HDL-cholesterol ratio, waist/hip ratio, systolic

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blood pressure (SBP) and anti-hypertensive treatment; model 2), and socio-demographic and lifestyle risk factors (smoking, manual occupation, physical activity and fruit and vegetable intake; model 3). Interactions between pre-diabetes or diabetes and ethnicity were sought in all models. Informative censoring may have occurred due to death from non-CVD causes; we addressed this by using competing risks regression (competing risk=death from non-CVD cause), based on Fine and Grey proportional subhazards methods(25). Additionally, we examined Nelson-Aalen cumulative hazard plots of CVD by glycaemic categories to check for violations of the proportional hazards assumption; none were found.

Findings were further explored by comparing prevalence of CVD risk factors, medication use and resultant risk factor control by glycaemic status for each ethnic group at baseline and at follow-up, to establish whether disparities in these factors may have contributed to ethnic differences in pre-diabetes/ CVD associations. Since these comparisons suggested ethnic differences in lipid and blood pressure control by glycaemic status, we sought interactions between lipids and pre-diabetes in models of CHD and blood pressure and pre-diabetes in models of stroke. We compared rates of conversion from pre-diabetes to overt diabetes by pre-diabetes criterion and ethnicity, and sought to test whether greater conversion, and thus exposure to the hyperglycaemia of diabetes could account for ethnic differences observed in the association between pre-diabetes and CVD outcomes.

Sensitivity analyses were conducted by: a) adjusting models for subsequent diabetes development as a time-varying covariate(26)), b) excluding events within the first five years of follow-up and c) the inclusion of people with baseline CVD (adjusting for baseline CVD).

Results

We report findings from a subset of 1,336 Europeans and 1,139 South Asians without prevalent coronary heart disease (CHD) or stroke at baseline, with either a full set of baseline

HbA$_{1c}$, fasting and post-load glucose measurements, or known diabetes, and with follow-up data for CHD and stroke (figure 1). African Caribbeans were excluded due to small numbers. There were no consistent differences between participants for whom we did and did not have the full set of blood samples.

Overt diabetes was more prevalent, and cardiometabolic risk factors generally more adverse in South Asians than Europeans (table 1). South Asians had a higher prevalence of HbA$_{1c}$-defined pre-diabetes than Europeans, though prevalence was similar when impaired fasting glycaemia (IFG)/ impaired glucose tolerance (IGT) criteria were used. For both ethnic groups, the prevalence of pre-diabetes was over two-fold higher when defined by American Diabetes Association (ADA) HbA$_{1c}$ thresholds, as opposed to International Expert Committee (IEC) HbA$_{1c}$ thresholds or IFG/IGT..

Pre-diabetes was associated with an increased risk of CHD in Europeans, but not South Asians (table 2). Associations were strongest for IEC HbA$_{1c}$ -defined pre-diabetes. This association persisted after adjustment for CVD risk factors and for socio-demographic and lifestyle factors (table 3). Conversely, in South Asians, no measure of pre-diabetes was associated with CHD risk. This ethnic difference in association between pre-diabetes and CHD was significant as an interaction (p=0.008 in the cardiovascular risk factor-adjusted model). Of note, diabetes was similarly related to CHD in each ethnic group regardless of diagnostic criteria.

In contrast, no pre-diabetes measure was associated with stroke risk in Europeans, whereas for South Asians, all three measures were associated in age- and sex-adjusted models (table 3). After adjustment for CVD risk factors, only the IEC HbA$_{1c}$–defined pre-diabetes association retained significance, though associations for the other pre-diabetes measures remained of large magnitude. There was some evidence that this measure was more

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associated with stroke risk in South Asians than Europeans (ethnicity interaction p=0.11 in the cardiovascular risk factor-adjusted model). Corresponding with ethnic differences in pre-diabetes associations, overt diabetes also appeared to be more strongly associated with stroke risk in South Asians than Europeans, though again this was not significant as an interaction (p=0.18).

Findings for CVD reflected those for CHD, with strong associations for pre-diabetes observed in Europeans but not South Asians, particularly for the IEC HbA$_{1c}$ criterion (p=0.04 for ethnicity by pre-diabetes interaction).

An important potential explanation for the ethnic differences observed in the association between pre-diabetes and CVD outcomes is control of key CVD risk factors. At follow-up, a lower percentage of Europeans than South Asians with baseline pre-diabetes on lipid-lowering medication had a total cholesterol<5.0 mmol/l (55% vs. 92%, p=0.004 for IEC-defined pre-diabetes) or an LDL-cholesterol of <3.0 mmol/l (66% vs. 91%, p=0.03). Rates of lipid-lowering medication use were generally higher in South Asians than Europeans with baseline pre-diabetes (75% vs. 58%, 68% vs. 73%, 69% vs. 57% for IFG/IGT, IEC- and ADA-defined pre-diabetes respectively) (table 2, supplementary material). Adjusting for baseline lipids alone did not explain ethnic differences and there were no interactions between pre-diabetes and lipid measures on these outcomes.

Baseline diastolic, but not systolic pressure, was higher in South Asians than Europeans. But in addition, blood pressure control (defined as <140/90 mmHg for those on anti-hypertensives) was generally worse in South Asians than Europeans with pre-diabetes, both at baseline and at follow-up (tables 1 and 2, supplementary material). Further, both mean diastolic and systolic pressures were higher in South Asians than Europeans in those on treatment. No other baseline CVD risk factor appeared to be consistently worse in the pre-

diabetic state in one ethnicity than the other (table 1, supplementary material). Ethnic differences in associations between pre-diabetes and stroke remained when adjusted for baseline blood pressure and use of anti-hypertensive medication, and again there were no statistically significant pre-diabetes x blood pressure (systolic or diastolic) interactions in either ethnic group.

For participants with pre-diabetes at baseline, rates of conversion to overt diabetes were higher in South Asians than Europeans - 68% vs. 40%, p<0.001, 52% vs. 30%, p=0.006 and 44 vs. 23%, p<0.001 for IFG/IGT, IEC- and ADA-defined pre-diabetes respectively.

Sensitivity analyses adjusting for diabetes development as a time-varying covariate, excluding events within the first five years of follow-up and including people with baseline CVD (and adjusting for it) did not alter the main results (data not shown).

Conclusions

We show marked ethnic differences in associations between pre-diabetes and CVD. Pre-diabetes was related to both CHD and CVD risk in Europeans but not South Asians.Strongest associations were observed for IEC than for ADA and OGTT criteria. In contrast, only South Asians demonstrated an association between pre-diabetes and stroke. Associations persisted on multivariate adjustment and on accounting for differential rates of incident diabetes diagnosis. Ethnic differences in baseline and follow-up CVD risk factor control may account for our findings (lipids for CHD in Europeans and blood pressure for stroke in South Asians).

The greater prevalence of pre-diabetes when defined by HbA_{1c} as opposed to glucose-based criteria in South Asians, not observed in Europeans, correspond with previous findings(17). However, we do not corroborate suggestions that classifying a higher number of South Asians as having pre-diabetes when HbA_{1c} criteria are used results in a less discriminative

indicator of CVD risk(18), since for CHD, pre-diabetes by any criterion appeared unrelated in South Asians, and for stroke, pre-diabetes by all criteria was associated.

For Europeans, modest associations between pre-diabetes and CHD correspond with previous findings(6, 7). Associations between pre-diabetes by IEC HbA$_{1c}$ criteria and CHD were stronger than those for glucose, reflecting either greater reproducibility of HbA$_{1c}$(27), or better capture of fed-state glycaemic status which may more closely associate with CHD(10)). There are no comparable prospective data for South Asians. The INTERHEART case-control study reported a greater risk of myocardial infarction in the highest vs. lowest quintile of HbA$_{1c}$ in Western Europeans but not South Asians(28), the latter corroborated by cross-sectional data(29).

Elevated lipids are key determinants of CHD risk (30). Total and LDL-cholesterol in those on lipid-lowering medication at follow-up were higher in Europeans than South Asians with pre-diabetes in SABRE, reflecting findings in people with diabetes(31)). Poor lipid control in pre-diabetic Europeans may have contributed to excess CHD risks compared to normoglycaemic individuals (and conversely, better control in South Asians may account for the lack of excess CHD in pre-diabetes). Conversion rates from pre-diabetes to overt diabetes were higher in South Asians than Europeans, occurring at an earlier age(26). This may have resulted in more aggressive and long-standing lipid management. Another possibility is that South Asians respond better to lipid-lowering(32), though this appears unlikely(33).

No associations were found between pre-diabetes and stroke for Europeans, whereas strong associations were seen in South Asians for all three criteria. Previous studies of Europeans report weak associations between fasting glucose, post-load glucose, HbA$_{1c}$ and stroke(6, 7).

Stroke numbers were modest in SABRE, and may reflect better blood pressure control than historical cohorts.

However blood pressure control in those with pre-diabetes on anti-hypertensives was worse in South Asians than Europeans at both baseline and follow-up, suggesting suboptimal management of this key stroke risk factor (34). This may account for the positive association between pre-diabetes and stroke in South Asians, again related to higher diabetes conversion rates, since blood pressure appears harder to control in South Asians then Europeans with diabetes(35, 36).

As well as indicating likely progression to overt diabetes, incorporation of pre-diabetes into CVD risk scoring systems(14), or its use as a treatment target per se has been proposed(3, 4). However, the amalgamation of CHD and stroke risk may result in undertreatment of stroke risk in South Asians. Furthermore, our findings indicate that pre-diabetes is linked to overall CVD risk in Europeans only, and only for HbA_{1c}–defined pre-diabetes, questioning the adoption of pre-diabetes as a trigger for population-level primary prevention.

Mechanistically, these findings suggest that glycaemia may be more related to microvascular (stroke) than macrovascular (CHD) disease in South Asians than Europeans. We have described greater levels of retinal rarefaction(37), poorer microvascular responses to ischaemia(38) and more adverse cerebral circulatory autoregulation(39), and others report greater cerebral microvascular disease(40), in South Asians than Europeans, with evidence that the latter two findings were mediated by hyperglycaemia. Furthermore, we have shown that the South Asian excess of stroke is largely explained by diabetes, commensurate with the current study's results regarding pre-diabetes(16). However, it is unclear why non-diabetic glycaemia is not so obviously related to CHD in South Asians(28, 29).

This study is novel in comparing associations between pre-diabetes and CVD in South Asians and Europeans. Strengths include the use of three different diagnostic criteria for pre-diabetes. HbA_{1c} was not available on all participants at baseline and, as with any cohort study, loss to follow-up may have introduced bias. However, 88% of Europeans and 90% of South Asians were followed-up, and analyses comparing a) those with and without a full set of baseline bloods, and b) responders and non-responders did not detect bias. Bias may have arisen from exposure misclassification, especially given the high variability of glucose measurements(27), though this is less likely for HbA_{1c}. Whilst the study was well-powered for CHD and CVD analyses, the relatively small number of strokes made interpretation of associations more difficult, though internal validity was demonstrated, since associations between all pre-diabetes measures and stroke were similar. Confounders such as use of and response to anti-hypertensive and lipid-lowering medication will have varied over time. We attempted to address this by examination of follow-up clinic data. Finally, the South Asians in our study were of Indian origin, and may not necessarily apply to other South Asian sub-groups.

In summary, we show relations between pre-diabetes and CVD outcomes varied by pre-diabetes diagnostic criterion, type of CVD and ethnicity. Despite calls for pre-diabetes to be pro-actively identified and treated(3, 4), we found that only pre-diabetes by IEC criteria (HbA_{1c} 6.0-6.5% [42-48 mmol/mol]) in Europeans was linked with overall CVD risk. For South Asians, who experience greater pre-diabetes, greater rates of conversion to diabetes, and greater risks of CVD than Europeans, pre-diabetes was only clearly associated with stroke. These results need substantiating, with further exploration of contributory mechanisms and evaluation of screening and interventions in pre-diabetes, especially in South Asian groups.

Acknowledgements

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	Europeans	South Asians	p*
N	1,336	1,139	-
Age, years	53(47-59)	50(45-56)	<0.001
Women	186(14)	214(19)	0.001
Ever smoked	930(70)	277(25)	<0.001
Manual occupation	809(61)	822(74)	<0.001
Fruit/ vegetables most days	933(70)	782(69)	0.9
Physical activity, MJ/week	10(7-15)	9(4-12)	<0.001
BMI, kg/m^2	26.1±4.0	26.1±3.6	0.7
Waist/ hip ratio:			
Men	0.94±0.07	0.99±0.06	<0.001
Women	0.79±0.09	0.87±0.09	<0.001
Total cholesterol, mmol/l	6.1±1.14	5.9±1.05	<0.001
HDL-cholesterol, mmol/l	1.3(1.1-1.5)	1.2(1.0-1.4)	<0.001
Total/ HDL-cholesterol ratio	4.7(3.8-5.8)	4.9(4.1-6.0)	<0.001
LDL-cholesterol, mmol/l	4.0±1.0	3.8±0.91	<0.001
Triglycerides, mmol/l	1.4(1.0-2.1)	1.7(1.2-2.5)	<0.001
Systolic blood pressure, mmHg	123±17	125±18	<0.001
Diastolic blood pressure, mmHg	77±11	80±11	<0.001
Anti-hypertensive medication	113(8)	133(12)	<0.001
Glycaemic status: IFG/ IGT			
Normoglycaemia	1,125(84)	758(67)	<0.001
Pre-diabetes	128(10)	135(12)	0.07
Diabetes†	83(6)	246(22)	<0.001
Glycaemic status: HbA$_{1c}$ (IEC pre-diabetes criteria i.e. 6.0-6.5% [42-48 mmol/mol])			
Normoglycaemia	1,170(88)	691(61)	<0.001
Pre-diabetes	92(7)	174(15)	<0.001
Diabetes†	74(6)	274(24)	<0.001
Glycaemic status: HbA$_{1c}$ (ADA pre-diabetes criteria i.e. 5.7-6.5% [39-48 mmol/mol])			
Normoglycaemia	903(68)	434(38)	<0.001
Pre-diabetes	359(27)	431(38)	<0.001
Diabetes†	74(6)	274(24)	<0.001

Table 1. Baseline characteristics of participants in the SABRE study, by ethnicity. Data

are median (IQR), n (%) or mean±SD, *age- and sex-adjusted p for ethnic difference.

†Includes pre-existing and newly-diagnosed diabetes by relevant criteria. IFG=impaired

fasting glycaemia, IGT= impaired glucose tolerance, IEC= International Expert Committee,

ADA=American Diabetes Association

Glycaemia measure	Europeans			South Asians				
	Normo-glycaemia	Pre-diabetes	New or known diabetes	Normo-glycaemia	Pre-diabetes	p*	New or known diabetes	p†
CHD								
IFG/ IGT	276/1,125 (25)	39/128 (30)	37/83 (45)	253/758 (33)	47/135 (35)	0.50	137/246 (56)	0.83
HbA$_{1c}$ (IEC)	275/1,170 (24)	42/92 (46)	35/74 (47)	230/691 (33)	60/174 (34)	0.004	147/274 (54)	0.33
HbA$_{1c}$ (ADA)	207/903 (23)	110/359 (31)	35/74 (47)	137/434 (32)	153/431 (35)	0.26	147/274(54)	0.38
Stroke								
IFG/ IGT	85/1,125 (8)	12/128 (9)	11/83 (13)	53/758 (7)	17/135 (13)	0.15	46/246 (19)	0.12
HbA$_{1c}$ (IEC)	90/1,170 (8)	8/92 (9)	10/74 (14)	47/691 (7)	20/174 (11)	0.13	49/274 (18)	0.22
HbA$_{1c}$ (ADA)	68/903 (8)	30/359 (8)	10/74 (14)	25/434 (6)	42/431 (10)	0.10	49/274 (18)	0.13
CVD								
IFG/ IGT	334/1,125 (30)	47/128 (37)	42/83 (51)	275/758 (36)	55/135 (41)	0.84	148/246 (60)	0.98
HbA$_{1c}$ (IEC)	339/1,170 (29)	47/92 (51)	39/74 (53)	252/691 (36)	69/174 (40)	0.02	161/274 (59)	0.58
HbA$_{1c}$ (ADA)	253/903 (28)	133/359 (37)	39/74 (53)	146/434 (34)	175/431 (41)	0.65	161/274 (59)	0.76

Table 2. Distribution of incident cardiovascular disease by glycaemic status and ethnicity in the SABRE study. Data are number of events/ number of participants (%), *p for age- and sex-adjusted ethnic difference in pre-diabetes vs. normoglycaemia, †p for age- and sex-adjusted ethnic difference in diabetes vs. normoglycaemia. CHD=coronary heart disease, CVD=cardiovascular disease, IFG=impaired fasting glycaemia, IGT=impaired glucose tolerance, IEC=international expert committee, ADA=American Diabetes Association.

Glycaemia measure	Model	Europeans			South Asians				
		Normo-glycaemia	Pre-diabetes	New or known diabetes	Normo-glycaemia	Pre-diabetes	p§	New or known diabetes	p‖
CHD									
IFG/ IGT	1	1	1.19(0.85,1.69)	1.82(1.28,2.59) †	1	1.06(0.77,1.44)	0.50	1.86(1.50,2.30) ‡	0.83
	2	1	1.03(0.72,1.47)	1.21(0.81,1.82)	1	0.97(0.72,1.32)	0.69	1.60(1.26,2.04) ‡	0.66
	3	1	1.22(0.87,1.72)	1.80(1.26,2.57) †	1	1.06(0.77,1.45)	0.50	1.94(1.56,2.41) ‡	0.84
HbA₁c (IEC)	1	1	1.82(1.30,2.53) ‡	2.01(1.39,2.90) ‡	1	0.99(0.75,1.32)	0.004	1.73(1.40,2.14) ‡	0.33
	2	1	1.68(1.19,2.38) †	1.35(0.89,2.03)	1	1.00(0.75,1.33)	0.008	1.44(1.13,1.83) †	0.67
	3	1	1.80(1.29,2.52) †	2.00(1.38,2.88) ‡	1	0.99(0.74,1.32)	0.004	1.82(1.46,2.26)‡	0.38
HbA₁c (ADA)	1	1	1.22(0.97,1.54)	2.02(1.39,2.93) ‡	1	1.07(0.85,1.34)	0.26	1.80(1.41,2.28) ‡	0.38
	2	1	1.12(0.88,1.42)	1.31(0.86,1.99)	1	0.98(0.78,1.24)	0.25	1.42(1.09,1.87) †	0.66
	3	1	1.22(0.96,1.54)	1.98(1.36,2.89) ‡	1	1.03(0.81,1.30)	0.21	1.84(1.44,2.34) ‡	0.39
Stroke									
IFG/ IGT	1	1	0.92(0.51,1.68)	1.44(0.80,2.56)	1	1.75(1.03,2.98)*	0.15	2.65(1.84,3.93) ‡	0.12
	2	1	0.83(0.45,1.56)	1.15(0.59,2.27)	1	1.51(0.86,2.64)	0.21	2.22(1.45,3.40) ‡	0.09
	3	1	0.97(0.53,1.77)	1.57(0.88,2.82)	1	1.60(0.91,2.83)	0.27	2.64(1.79,3.89‡	0.17
HbA₁c (IEC)	1	1	0.91(0.47,1.75)	1.55(0.87,2.78)	1	1.80(1.09,2.97)*	0.13	2.59(1.69,3.72) ‡	0.22
	2	1	0.85(0.44,1.64)	1.30(0.67,2.54)	1	1.73(1.03,2.90)*	0.11	2.19(1.37,3.25) ‡	0.18
	3	1	0.92(0.48,1.76)	1.67(0.94,3.00)	1	1.66(1.00,2.79)*	0.20	2.50(1.67,3.73) ‡	0.33
HbA₁c (ADA)	1	1	0.97(0.65,1.45)	1.56(0.86,2.84)	1	1.69(1.05,2.72)*	0.10	2.93(1.83,4.69)v	0.13
	2	1	0.95(0.63,1.43)	1.31(0.66,2.59)	1	1.60(0.98,2.62)	0.12	2.51(1.52,4.14) ‡	0.12
	3	1	0.95(0.64,1.42)	1.66(0.92,3.02)	1	1.64(0.99,2.70)	0.13	2.93(1.81,4.72) ‡	0.20
CVD									
IFG/ IGT	1	1	1.17(0.86,1.60)	1.73(1.24,2.41) †	1	1.16(0.87,1.54)	0.84	1.83(1.49,2.25) ‡	0.98
	2	1	1.03(0.74,1.42)	1.22(0.83,1.79)	1	1.05(0.79,1.40)	0.99	1.58(1.25,1.98) ‡	0.51
	3	1	1.20(0.88,1.64)	1.75(1.25,2.45) †	1	1.12(0.83,1.51)	0.68	1.91(1.54,2.36) ‡	0.94
HbA₁c (IEC)	1	1	1.61(1.18,2.20) †	1.85(1.30,2.63) †	1	1.06(0.81,1.38)	0.02	1.77(1.44,2.17) ‡	0.58
	2	1	1.49(1.08,2.07)*	1.31(0.88,1.95)	1	1.03(0.78,1.36)	0.04	1.45(1.15,1.83) †	0.97
	3	1	1.61(1.17,2.21) †	1.88(1.32,2.67) ‡	1	1.03(0.78,1.36)	0.02	1.82(1.48,2.25) ‡	0.59
HbA₁c (ADA)	1	1	1.21(0.98,1.49)	1.88(1.31,2.68) †	1	1.19(0.96,1.48)	0.65	1.90(1.51,2.40) ‡	0.76
	2	1	1.12(0.90,1.39)	1.30(0.87,1.94)	1	1.08(0.87,1.36)	0.63	1.51(1.17,1.96) †	0.87
	3	1	1.20(0.97,1.49)	1.89(1.32, 2.70) ‡	1	1.12(0.90,1.41)	0.48	1.93(1.52,2.44) ‡	0.69

Table 3. Competing risks regression models of incident cardiovascular disease by glycaemic status and ethnicity; the SABRE study. Data are sub hazards ratios (95% CI), *p<0.05, †p<0.01, ‡p<0.001. p for ethnic difference: §pre-diabetes vs. normoglycaemia, ||diabetes vs. normoglycaemia. Model 1: age, sex, model 2: age, sex, smoking, total/HDL-cholesterol, waist/hip ratio, SBP, anti-hypertensives, model 3: age, sex, smoking, manual occupation, physical activity and fruit and vegetable intake. CHD=coronary heart disease, CVD=cardiovascular disease, IFG=impaired fasting glycaemia, IGT=impaired glucose tolerance, IEC=international expert committee, ADA=American Diabetes Association.

Figure legends

Figure 1. Follow-up of the SABRE cohort 1988-2011. CVD=cardiovascular disease,

FPG=fasting plasma glucose, PLG=post-load glucose.